

Metabolic Risk Factors in Prostate Cancer

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Metabolic syndrome and prostate cancer (pCa) remain 2 growing health problems affecting millions of men. Although various metabolic syndrome 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 pCa with various metabolic syndrome components, future research must be directed toward combating both diseases and understanding their interplay.

To this end, Van Hemelrijck et al examined the relation between pCa risk and various metabolic syndrome components in the large prospective AMORIS cohort from Sweden: >200,000 pCa-free men of various ages were followed for ≥ 7 years until death, the study closing date, or pCa diagnosis, which occurred in 5112 men. The primary outcome was pCa risk as a function of baseline triglycerides, total cholesterol, and glucose levels drawn within 10 years before cohort entry. Greater than 60% of these measurements were taken on fasting patients. The authors found men with higher glucose had lower pCa risk. Moreover, elevated triglycerides were associated with greater pCa risk but only in men with high glucose. Last, the authors graphically showed that non-pCa-related mortality may alter the observed associations between metabolic factors and pCa. Given that men who die of other causes are no longer at risk for pCa, one must account for this competing risk. The authors suggest that because of this competing risk, the association between high glucose and reduced pCa risk may be overestimated, whereas the association between high triglycerides and elevated pCa risk in hyperglycemic men may be underestimated.

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

Importantly, Van Hemelrijck et al's findings reinforce the hypothesis that pCa 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 metabolic syndrome. Although the exact interplay among these factors and pCa remains unclear, they all have important clinical implications for future directions in pCa research and ultimately pCa prevention and treatment. Although Van Hemelrijck et al did briefly mention these factors, they all are worthy of further discussion in the context of pCa risk.

Glucose, Insulin, and IGF-1

The association between high glucose and reduced pCa risk found by Van Hemelrijck et al underscores the finding that diabetes (characterized by high fasting glucose) is consistently linked to lower pCa risk.¹ In 1 multiethnic cohort of >86,000 men, diabetics had significantly lower pCa risk and significantly lower prostate-specific antigen (PSA) levels versus non-diabetics.³ Another study noted that the time since diabetes diagnosis significantly affected pCa risk in a cohort of >72,000 men and found a positive association between pCa risk and being diagnosed with diabetes <4 years before pCa

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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 to low insulin due to damaged pancreatic beta cells. Because elevated insulin is strongly implicated in pCa growth and mortality,⁵ long-standing diabetics, with their lower insulin, may be protected from pCa.

The clinical implications of this protective effect of diabetes on pCa are controversial. As diabetic men have lower PSA levels than nondiabetic men,³ a detection bias may exist in pCa 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 pCa presence or absence regardless of PSA and found decreased pCa risk in diabetics. In addition, the same study showed a 28% reduced high-grade pCa risk in diabetics versus nondiabetics,⁶ which is unexpected if diabetic men truly suffer from delayed diagnosis. Thus, the meaningfulness of lower PSA in diabetic men remains unclear.

Closely related to insulin, IGF-1 is a pCa mitogen. Clinical data strongly implicate IGF-1 in increased pCa risk.⁷ A recent meta-analysis encompassing 42 studies and >7400 pCa cases confirmed a significant positive association between elevated IGF-1 levels and pCa risk, with weak evidence of an association with advanced-stage disease.⁷ Additional evidence comes from translational research in mouse models, which have highlighted the effect of IGF-1 levels 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, an attenuated prostatic androgenic response.⁹ Therefore, IGF-1 may affect pCa growth by serving as a link between the insulin and the androgen axes.

Testosterone

The dependence of pCa on androgens is well established. Not surprisingly, therefore, conventional wisdom has thought testosterone should be associated with pCa risk. Although initial studies suggested pCa 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 relation 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 pCa 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 metabolic syndrome,¹⁴ all of which have key implications in determining pCa risk. A meta-analysis of studies linking diabetes and sex-steroid hormones found that men with higher testosterone had a 42% decreased diabetes risk versus men with lower levels.¹³ In addition, a recent meta-analysis of 21 studies found that testosterone-replacement therapy in hypogonadal men drastically improved many metabolic syndrome components, including reduced triglycerides, glucose, insulin resistance, and waist circumference, and increased HDL levels.¹⁴ These effects are also seen in men undergoing hormone therapy for pCa (ie, 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 its crucial interplay with other pCa metabolic risk factors, may be a critical mediator in the regulation and treatment of not only metabolic syndrome and its components but also of pCa.

Triglycerides

High triglycerides may be a pCa risk factor, although results are mixed. Although Van Hemelrijck et al found a positive association between high triglycerides and pCa risk in men with high glucose levels, other investigators have found no relation between high triglycerides and pCa 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 whereas diabetic men with ≥ 2 other metabolic syndrome components had a 23% reduced pCa risk, nondiabetic men with 2 metabolic syndrome components had a 37% significantly *increased* risk versus men without any metabolic syndrome components.¹⁶ Therefore, the protective effect of insulin resistance and diabetes may obscure the effects of hypertriglyceridemia and, in general, the overall effects of metabolic syndrome on pCa risk. Moreover, to help

explain why Van Hemelrijck et al found a positive association between high triglycerides and pCa 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 pCa risk,¹⁷ has been clearly linked with aggressive pCa¹⁸ and worse cancer-specific survival.¹⁹

Cholesterol

As the molecular skeleton of all steroids, including androgens, cholesterol has been studied extensively in pCa. 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 pCa.²¹ One large study from the PCPT placebo arm found a strong correlation between lower cholesterol and lower risk of high-grade pCa.²¹ Moreover, the strongest evidence to support the role of cholesterol in pCa risk comes from 4 large prospective studies showing that statins, drugs which lower serum cholesterol levels, were associated with similar reductions in advanced pCa risk but not in overall pCa risk.²² Thus, while Van Hemelrijck et al did not find an association for high cholesterol with overall pCa risk, their study did not distinguish high-grade from low-grade tumors.

Conclusion

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

significant non-pCa-related morbidity and mortality in the next generation, is urgent.

CONFLICT OF INTEREST DISCLOSURES

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