CORRESPONDENCE

Re: Insulin Resistance and Prostate Cancer Risk

In three papers from the same case–control series recruited from Shanghai, China, Hsing et al. (1–3) have reported statistically significant associations between prostate cancer risk and aspects of insulin resistance syndrome. First, they observed an increase in prostate cancer risk associated with abdominal obesity, measured by waist-to-hip ratio (odds ratio [OR] = 2.71 for highest versus lowest quartile) (1). Subsequently, they reported an OR of 2.80 for highest versus lowest tertile of insulin (2), and they reported an OR of 2.78 for highest versus lowest tertile of an index of insulin resistance, calculated from fasting insulin and blood glucose levels in a homeostasis model (HOMA IR) (3). Equivalent results, but in the opposite direction, were found for an index of insulin sensitivity, instead of insulin resistance, calculated as “QUICKI.” Hsing et al. pointed out the need for prospective studies on insulin resistance syndrome and prostate cancer risk.

Prompted by the work of Hsing et al. (1–3), we re-analyzed our data from The Northern Sweden Health and Disease Cohort, in which prostate cancer risk was not associated with body mass index (BMI) or insulin in blood samples collected, on average, 4 years before cancer diagnosis (4). We then calculated the ORs for indices of insulin resistance (HOMA IR) and insulin sensitivity (QUICKI), and we found no association between these indices or insulin levels and prostate cancer risk (Table 1). Given the strong correlation between insulin and HOMA IR (Spearman coefficient of correlation, r = .95) and between insulin and QUICKI (r = -.95) in our study, it is not surprising that all three measures resulted in very similar risk estimates.

The Chinese study subjects in the studies by Hsing et al. (1–3) had a substantially lower mean BMI than the Swedish study subjects (21 kg/m² versus 26 kg/m²), were older at recruitment (71 years versus 59 years), and were more frequently smokers (60% versus 20%). The Chinese case subjects had a much higher percentage of nonlocalized disease (64% versus 11%) and high-grade tumors (37% versus 13%) than the Swedish case subjects. The distribution of BMI and tumor stage and grade in the Swedish study group was similar to that in cohorts from Europe and the United States (5,6).

Possibly, prostate cancer risk is associated with insulin only at the lower end of the scale of insulin resistance and BMI, but not at levels common in subjects from Europe and the United States.

BMI, a strong determinant of insulin resistance, has not been strongly associated with prostate cancer risk in Western populations (7). Alternatively, aggressive disease, which was more common in the Chinese study, may have a stronger association with hormonal changes than less aggressive disease. To what extent the results from the Chinese study subjects can be extrapolated to men in Western countries, or may explain the higher incidence rates in the West, remains to be elucidated.

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REFERENCES


![Table 1. Associations between prostate cancer risk and plasma insulin, indices of insulin resistance (HOMA IR), and insulin sensitivity (QUICKI) in a case–control study of 135 Swedish men](image)

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<thead>
<tr>
<th>Tertile*</th>
<th>Categories</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
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<tr>
<td>No. of case patients/No. of control subjects</td>
<td>1.00 (referent)</td>
<td>1.12 (0.67 to 1.88)</td>
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<tr>
<td>Mean (μU/mL)</td>
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<td>46/85</td>
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<td>HOMA IR†</td>
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<td></td>
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<tr>
<td>No. of case patients/No. of control subjects</td>
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<tr>
<td>Mean</td>
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<td>49/85</td>
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<tr>
<td>QUICKI‡</td>
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<td></td>
</tr>
<tr>
<td>No. of case patients/No. of control subjects</td>
<td>1.00 (referent)</td>
<td>1.46 (0.86 to 2.47)</td>
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<tr>
<td>Mean</td>
<td>40/94</td>
<td>49/86</td>
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*Odds ratios and 95% confidence intervals in an analysis of 135 matched case–control subjects were determined by conditional logistic regression with available measurements of insulin and glucose (4).
†HOMA-IR index = homeostasis assessment model of insulin resistance; (I₀ [μU/mL] × G₀ [mmol/L])/22.5, where I₀ = fasting insulin measured in plasma by an immunoradiometric assay (Immunotech, Marseille, France) and G₀ = fasting glucose by the hexokinase method (Boehringer Mannheim, Mannheim, Germany) (3,4).
‡QUICKI = quantitative insulin sensitivity check index: 1/(log I₀ [μU/mL] + log G₀ [mmol/L]). Adjustment for fasting, body mass index, and smoking did not essentially alter the odds ratios. Fasting times were greater than 8 hours for 65% of the subjects and 4–8 hours for 37%; smoking was coded as current smoker, past smoker, and never smoker.

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We agree with Drs. Stattin and Kaaks that our earlier findings associating abdominal obesity, hyperinsulinemia, and insulin resistance with prostate cancer risk in Chinese men with a relatively low body mass index (BMI; average BMI = 21 kg/m²) cannot be readily extrapolated to Western men and that these associations need to be replicated in prospective studies and other populations. In their nested case–control study of Swedish men, Drs. Stattin and Kaaks showed no association between insulin resistance and prostate cancer risk. They pointed out that a number of factors, including differences in study design, clinical characteristics of case subjects, selection of control subjects, prevalence of overall and abdominal obesity, and genetic susceptibility, could contribute to the differences in findings between their study and ours. Because of the much higher average BMI in the Swedish study (average BMI = 26 kg/m²) and the small number of case subjects, it was difficult to restrict the analysis to men with a BMI below 25 kg/m² (the cutoff for overweight) or even lower, which would have yielded results more comparable to ours. In addition, among overweight or obese individuals, it may be more difficult to detect the effect of insulin resistance because of potential changes in their metabolic profiles.

Although the evidence for a role of overall obesity (measured by BMI) in prostate cancer is not conclusive, data in the literature generally suggest a link between obesity and more aggressive and advanced prostate tumors (1). Recently, a large prospective study of more than 400,000 U.S. men and 4004 prostate cancer deaths reported a 34% excess prostate cancer risk among men in the highest quartile of BMI (>35 kg/m²), relative to those in the lowest quartile (2). These results further support the obesity–prostate cancer hypothesis.

It is possible that abdominal obesity may play a more important role in prostate cancer than overall obesity, and differences in the prevalence of abdominal obesity and genetic susceptibility between Asian and Western men may partially explain the differences in study findings. Although Chinese men are generally considered to be relatively lean (only 4% had a BMI >30 kg/m² in our study), 24% of our study subjects had abdominal obesity (as measured by a waist-to-hip ratio >0.90) (3), and a small subset were considered to be metabolically obese (individuals with insulin resistance despite having a normal weight) (4). Asian men, in particular Southeast Asians and Asian Indians, despite their much lower BMI, are much more prone to develop insulin resistance than Caucasian men (5). In a study of African and Hispanic American men in the Bronx, we reported that a polymorphism of the insulin gene (INS) is associated with prostate cancer; men without diabetes but harboring the homozygous CC genotype of +1127 INS-PstI have a threefold increased risk of prostate cancer (6). Whether Asian men with certain genetic predispositions are at higher risk of developing prostate cancer is currently unclear and needs to be elucidated further.

Given the rising global epidemic of obesity and the high morbidity of prostate cancer, the role of obesity and insulin resistance needs to be clarified in large prospective studies with high-quality exposure assessment. Such studies should be large enough to permit testing of the obesity hypothesis and, at the same time, take into account the effect of other factors, such as physical activity, energy balance, insulin-like growth factors, sex hormones, and genetic susceptibility. These studies will help us to achieve a better understanding of the overall picture of prostate cancer etiology and the complex interplay between lifestyle and genetic factors.

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