Re: Plasma Insulin-Like Growth Factor-I, Insulin-Like Growth Factor-Binding Proteins, and Prostate Cancer Risk: a Prospective Study

The important article by Stattin et al. (1) provides further evidence that insulin-like growth factor-I (IGF-I) may play a key role in the development of prostate cancer. Prediagnostic levels of serum IGF-I were, on average, 7% higher in men who subsequently developed prostate cancer compared with healthy individuals, a result similar to that found in the Physicians’ Health Study (2).

Circulating IGF-I levels have been shown to be sensitive to nutritional factors: A diet severely restricted in energy and/or protein intake substantially reduces serum IGF-I concentrations in both animals and humans (3). Stattin et al. (1) suggest that elevated IGF-I levels could be a potential mechanism through which a Western high-energy diet may increase prostate cancer risk. However, they acknowledge that obesity is not related to an increase in IGF-I concentration and that a high body mass index is not a strong risk factor for prostate cancer.

An alternative explanation is that protein intake may be the critical determinant of IGF-I serum concentrations that ultimately influence prostate cancer risk. The rationale is that a diet low in protein and essential amino acids will reduce IGF-I production and thereby reduce the growth of prostate cancer from a latent to a clinically manifest form. One test of this hypothesis is to examine IGF-I levels among men who consume a vegan diet, which contains only plant protein and, therefore, fewer essential amino acids than diets containing primarily animal protein (4). We have recently shown that the mean serum IGF-I concentration was 9% (95% confidence interval = 6% to 13%) lower among 233 vegan men who consumed no animal products than it was among either 237 lacto-ovo-vegetarians, who consumed no meat or fish but did consume either dairy and/or egg products, or 226 meat eaters (5). Among the 696 men studied, consumption of a diet rich in essential amino acids (i.e., containing protein derived from animal and soy products) was positively correlated with serum IGF-I concentrations. Serum IGF-I concentration increased 20% from 17.4 nmol/L in the lowest decile of intake (<9.7 g/day of animal and soy protein) to 20.8 nmol/L in the highest decile of intake (≥74.5 g/day of animal and soy protein after adjustment for age, body mass index, smoking, vigorous exercise, and factors related to blood collection (test for linear trend; P = .007). These results suggest that the low essential amino acid intake among vegan men may explain their low serum IGF-I concentrations. It is important to note that total protein, total energy intake, and body mass index were not statistically significantly associated with IGF-I concentration in this population.

An epidemiologic study (6) has shown that mortality due to prostate cancer is correlated with per capita consumption of both animal fat and animal protein. However, studies on the role of animal fat in prostate cancer development [reviewed in (7)] have produced inconsistent results. The increasing evidence that small differences in serum IGF-I concentrations are associated with prostate cancer risk and the sensitivity of IGF-I concentration to protein intake suggest that differences in dietary intake of animal protein may partly explain the wide international variation in prostate cancer mortality.

References

Kolonel LN, Nomura AM, Cooney RV. Increased, rather than increased, levels of IGF-I proteins, and especially of essential amino acids, is a key determinant of circulating IGF-I concentrations and diets rich in animal protein and associated essential amino acids. This very interesting observation is in line with results from several intervention studies in humans that showed that the intake level of protein, and especially of essential amino acids, is a key determinant of circulating levels of IGF-I. On the contrary, a comparatively elevated BMI (>30 kg/m²) is associated with decreased, rather than increased, levels of IGF-I. Nevertheless, we would not rule out the existence of a positive association between IGF-I and adiposity in populations where the majority of subjects have a BMI below 22–24 kg/m², as is the case in many developing countries where prostate cancer risk is low. This would imply a nonlinear relationship between adiposity and IGF-I levels, with peak levels of IGF-I occurring in individuals with a BMI of about 25 kg/m², and a gradual decrease at higher levels of adiposity. This hypothesis—that increasing IGF-I levels accompany increasing adiposity in nonobese individuals—fits with observations made in patients with anorexia nervosa and also fits with observations that only a minimum level of endogenous insulin is required for tissues to respond optimally to growth hormone, the principal stimulus for IGF-I synthesis (5,6). In contrast, obesity and chronic hyperinsulinemia decrease pituitary growth hormone secretion and, hence, cause a drop in the level of IGF-I (3).

Recent analyses in our Umeå cohort give some additional support to the hypothesis of a nonlinear relationship between IGF-I concentrations and adiposity. Although there was no significant linear correlation (r = 0.3) between BMI and IGF-I levels, we did observe a slight increase in IGF-I levels from the first to the third quintile of BMI as well as a slight decrease in IGF-I levels from the third to the fifth quintile of BMI (Table 1). We also analyzed the relationship between levels of IGF-I and of leptin, a molecule that may reflect adiposity more directly than BMI, and found a similar nonlinear association between levels of IGF-I and leptin both in men (Table 1) and in women (data not shown). It is interesting that we also observed a statistically significant increase in prostate cancer risk for the second and third quintiles of leptin concentration (7), although BMI was unassociated with prostate cancer risk.

There is still a surprising lack of observational and intervention studies in humans that confirm the possible relationship between animal protein consumption and IGF-I levels; further studies are required to confirm such a relationship. Further studies are also needed to compare IGF-I levels between lean populations with low energy intake (and low prostate cancer risk) in developing countries and well-nourished (or overnourished) population groups in more affluent societies.

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REFERENCES

(5) Counts DR, Gwirtsman H, Carlsson LM, Lesem M, Cutler GB. The effect of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors

Table 1. Age-standardized, mean plasma IGF-I concentrations (ng/mL) by quintiles of BMI and leptin

<table>
<thead>
<tr>
<th>Quintile level†</th>
<th>BMI</th>
<th>% difference from quintile with highest IGF-I level‡</th>
<th>Leptin</th>
<th>% difference from quintile with highest IGF-I level§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>220.3</td>
<td>−7</td>
<td>216.5</td>
<td>−7.7</td>
</tr>
<tr>
<td>2</td>
<td>227.0</td>
<td>−3.9</td>
<td>233.2</td>
<td>±0</td>
</tr>
<tr>
<td>3</td>
<td>235.9</td>
<td>±0</td>
<td>227.7</td>
<td>−2.4</td>
</tr>
<tr>
<td>4</td>
<td>219.3</td>
<td>±0</td>
<td>221.9</td>
<td>−5.1</td>
</tr>
<tr>
<td>5</td>
<td>203.6</td>
<td>±0</td>
<td>207.1</td>
<td>−12.6</td>
</tr>
</tbody>
</table>

*IGF-I = insulin-like growth factor I; BMI = body mass index.
†Quintile cut points for BMI were 23.6, 25.3, 26.8, and 28.7 kg/m². Quintile cut points for leptin were 2.7, 3.9, 5.4, and 8.4 ng/mL.
‡P values are two-sided. We tested for an overall association of IGF-I with quintile of BMI or leptin in a generalized linear regression model, adjusted for age and case–control status.
§The difference between the mean levels of IGF-I for each quintile level and the quintile with the highest mean IGF-I level (quintile 3 for BMI and quintile 2 for leptin) divided by the mean level of IGF-I for that quintile.

NOTES

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RESPONSE

Drs. Allen and Key present evidence that suggests a relationship between serum IGF-I concentrations and diets rich in animal protein and associated essential amino acids. This very interesting observation is in line with results from several intervention studies in humans that showed that the intake level of protein, and especially of essential amino acids, is a key determinant of circulating IGF-I levels (1,2). We share the view of Drs. Allen and Key that an elevated intake of animal protein might, at least partly, explain the high incidence rates of prostate cancer in westernized, industrial countries.

A parallel hypothesis is that the balance between energy intake and expenditure also affects circulating IGF-I levels, which in turn affect prostate cancer risk. However, the relationship between plasma levels of IGF-I, prostate cancer, and adiposity (as a result of high energy intake and low expenditure) is complex. Results from a large number of epidemiologic studies [reviewed in (3)] have shown no consistent relationship between prostate cancer risk and body mass index (BMI). Furthermore, cross-sectional studies [reviewed in (4)] have also not shown a simple, direct relationship between BMI and circulating levels of IGF-I. On the contrary, a comparatively elevated BMI (>30 kg/m²) is associated with decreased, rather than increased, levels of IGF-I (4). Nevertheless, we would not rule out the existence of a positive association between IGF-I and adiposity in populations where the majority of subjects have a BMI below 22–24 kg/m², as is the case in many developing countries where prostate cancer risk is low. This would imply a nonlinear relationship between adiposity and IGF-I levels, with peak levels of IGF-I occurring in individuals with a BMI of about 25 kg/m², and a gradual decrease at higher levels of adiposity. This hypothesis—that increasing IGF-I levels accompany increasing adiposity in nonobese individuals—fits with observations made in patients with anorexia nervosa and also fits with observations that only a minimum level of endogenous insulin is required for tissues to respond optimally to growth hormone, the principal stimulus for IGF-I synthesis (5,6). In contrast, obesity and chronic hyperinsulinemia decrease pituitary growth hormone secretion and, hence, cause a drop in the level of IGF-I (3).

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