

Serum Insulin-like Growth Factor I: Tumor Marker or Etiologic Factor? A Prospective Study of Prostate Cancer among Finnish Men¹

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ABSTRACT

Recent epidemiological studies suggest an association between higher blood levels of insulin-like growth factor I (IGF-I) and increased risk of prostate cancer. We evaluated the association between prediagnostic levels of IGF-I and insulin-like growth factor binding protein 3 (IGFBP-3) and prostate cancer risk in a nested case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Within the same cohort (using different cases and controls who had sequential serum samples available) we also examined changes in serum IGF-I and IGFBP-3 levels over time by case status. The risk association study included incident prostate cancer cases ($n = 100$) diagnosed at least 5 years after baseline blood draw (range, 5–12 years; median 9 years) and frequency-matched (4:1) controls. The sequential serum study included all of the prostate cancer cases ($n = 21$) with prediagnostic (2–3 years before diagnosis) and diagnostic serum available, and pair-matched controls (1:1). An ELISA was used to quantitate serum levels of IGF-I and IGFBP-3 for both studies. The association between IGF-I or IGFBP-3 and prostate cancer risk was assessed using conditional logistic regression, and paired t tests were used to evaluate case-control differences in change in serum analytes over time. We found no significant association between either IGF-I or IGFBP-3 and prostate cancer risk. In a multivariate analysis, we observed an odds ratio of 0.52 (95% confidence interval, 0.23–1.16) for the fourth versus the first quartile of serum IGF-I. Serum IGF-I, but not IGFBP-3, increased significantly over time in cases (18% increase) but not controls (4% decrease; $P = 0.02$). In contrast to previous reports, we found no evidence to support a causal association between serum IGF-I or IGFBP-3 and the risk of prostate cancer. It is possible that serum IGF-I may be serving as a tumor marker rather than an etiologic factor in prostate cancer.

INTRODUCTION

IGFs³ are mitogenic peptides involved in the regulation of cell proliferation, differentiation, and apoptosis in a wide variety of cells and tissues (1). IGFs have a structure similar to that of proinsulin and contribute to the proliferation of cells by binding to cell-surface receptors. Exogenous IGF-I has been shown to stimulate proliferation of both normal and transformed prostate epithelial cells in *in vitro* and *in vivo* models (2–4).

Bioavailability of IGFs is modulated by six IGFBPs. Circulating IGF-I and most of the IGFBPs are produced in the liver, through stimulation by growth hormone (5). Circulating IGF-I levels vary

throughout life, increasing from birth to pubertal peak and decreasing steadily after 30 (1). By binding to IGF-I, the IGFBPs inhibit the binding of IGF-I to its receptor and reduce “free” IGF-I levels. The bioactivity of IGF-I is determined by circulating levels of IGF-I as well as its production within tissues. Thus, IGF-I bioavailability is thought to be predominantly regulated by IGFBP-3 given that the latter has the highest blood concentrations among the IGFBPs (5), and is bound to >90% of circulating IGF-I (6). In addition to potentially modulating cancer growth by reducing free IGF-I, IGFBP-3 may also affect carcinogenesis through IGF-I independent mechanisms (7).

Recent epidemiological studies suggest an association between elevated blood levels of IGF-I and increased risk of prostate cancer, although the data are inconsistent across studies (8–13). Of the three prospective observational studies (8–10), only one found a significant positive association with serum IGF-I, observing that serum IGF-I levels were 9% higher in cases than controls (8). However, all of the published retrospective studies (where blood was drawn close to case diagnosis) reported significant case-control differences in serum IGF-I, ranging from 8% to 29% higher in the cases (11–13). In general, circulating levels of IGFBP-3 have not been associated with prostate cancer risk (8, 12, 13).

Although some studies suggest an association, a causal link has not been established between circulating IGF-I and prostate cancer. It is still not clear whether elevated serum IGF-I levels observed in prostate cancer patients are in the causal pathway or are simply a reflection of the presence of undetected tumor. To minimize the influence of preclinical prostate disease on serum IGF-I levels, we conducted a prospective case-control study nested within a cohort of male participants of a large cancer prevention trial and included only those prostate cancer cases diagnosed from 5–12 years after blood collection (termed the RAS). In addition, to also elucidate the effect of prostate tumor on serum IGF-I levels, we conducted another small study within the same cohort using different cases and controls who had sequential serum samples available. We examined changes in serum IGF-I levels over time by case status (using a sample of blood collected at or near time of case diagnosis and another sample collected from 2 to 5 years before case diagnosis; termed the SSS).

MATERIALS AND METHODS

Sample Population and Data Collection. The ATBC Study was conducted in Finland between 1985 and 1993 as a joint project between the National Public Health Institute in Finland and the United States National Cancer Institute. The large, double-blind, randomized, placebo-controlled prevention trial was designed to determine whether daily supplementation with tocopherol (50 mg daily), carotene (20 mg daily), or both would reduce the incidence of lung or other cancers. The overall design and initial results have been published (14, 15). Briefly, the participants ($n = 29,133$) were male smokers who were 50–69 years old at entry; they were recruited from the total male population of this age group in 14 geographic areas in southwestern Finland ($n = 209,406$). α -Tocopherol was associated with a 32% reduction in prostate cancer risk. At baseline, study participants completed a general risk factor and medical history questionnaire that included usual diet and activity;

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³ The abbreviations used are: IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; RAS, risk association study; SSS, sequential serum study; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention; OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate specific antigen.

height, and weight were measured, and serum samples were collected. In addition, serum was collected from a random sample of 800 men annually throughout the course of the trial.

Case-Control Selection. For the RAS, cases included a random selection of men with incident prostate cancer from the ATBC Study cohort ($n = 100$) diagnosed at least 5 years after baseline blood draw (range, 5–12 years; median, 9 years) to minimize any effect of preclinical disease on serum measurements. All of the cases were confirmed in a central review of medical records, and histopathologic and cytologic specimens by an ATBC study physician in Finland. Thirty percent of the prostate cancer cases were diagnosed with extracapsular disease (stage III-IV). Only ~25% of the cases had tumors considered to be poorly differentiated (grade 3, roughly equivalent to Gleason grade 7–10). Controls were randomly selected from members of the cohort.

For the SSS, we selected all 21 of the prostate cancer cases from the ATBC cohort who had serum drawn at or near the time of cancer diagnosis (within 1 year before diagnosis) and also had a second serum sample drawn from 2–5 years before diagnosis (average, 3 years). Controls were selected from those trial participants who had no cancer diagnosed (except nonmelanoma skin cancer) over the full period of study follow-up (up to April 1999) and had two serum draws at least 1 year apart (average, 3 years). Cases and controls were matched 1:1 on age (± 5 years), intervention group, and time between blood draws (± 6 months). Cases and controls chosen for the SSS were distinct from those selected for the RAS. The distribution of tumor grade and disease stage of the SSS cases was similar to those in the RAS case set. The cases and controls from the SSS set were slightly older than those in the RAS set (mean baseline age 61.1 for cases and 60.8 for controls of the SSS set compared with 59.0 and 56.4 for cases and controls of the RAS set, respectively).

IGF-I and IGFBP-3 Assays. Serum levels of IGF-I and IGFBP-3 were assayed by ELISA. Samples from case subjects and their matched controls were assayed as pairs consecutively and in the same batch to minimize interassay variability. For quality control, aliquots from a single pooled serum sample were randomly placed within each batch. For the RAS, serum analytes were assayed with reagents from Diagnostic Systems Laboratory (Webster, TX) in the laboratory of M. P. The overall coefficients of variation of QC serum factors in the RAS were 6.6% for IGF-I and 7.3% for IGFBP-3. Given the study sample size and these coefficients for variation, the RAS has >90% power with a two-side α of 0.05 to detect a 15% difference of means for both IGF-I and for IGFBP-3. Approximately 1 year after analysis of RAS samples, sera from SSS participants were analyzed for IGF-I, IGFBP-3, and PSA by ELISA using R&D Systems assays (Minneapolis, MN) at the Protein Chemistry Core, Basic Research Laboratory (National Cancer Institute, Frederick, MD). The overall coefficients of variation for IGF-I, IGFBP-3, and PSA in the SSS were 7.1%, 6.4%, and 9.9%, respectively.

Serum values for IGF-I but not IGFBP-3 were significantly lower in the SSS sample set compared with the RAS set. In addition to the use of a different set of cases and controls in the SSS, these differences could also be attributed to the combination of the use of different laboratories and ELISA reagents (different supplier) in the two studies. However, this would not affect the internal validity of the SSS, because both cases and controls were assayed within the same batch in the same laboratory and the statistical analysis is based on relative differences and not absolute IGF-I levels. Furthermore, internal quality control standards show that the IGF-I ELISA assays for both the SSS and RAS performed equally well (coefficients of variation ~7%).

Statistical Analysis. The characteristics of case and control subjects were compared by the nonparametric Wilcoxon rank sum test for continuous variables, and χ^2 test for categorical variables. For the RAS, ORs and 95% CIs for the association between serum IGF-I and IGFBP-3 and prostate cancer were determined in logistic regression models. Potential confounders were assessed by evaluating their associations with serum IGF-I or IGFBP-3 and prostate cancer. Final models were adjusted for age (as a continuous variable), BMI (as a continuous variable), and intervention assignment. Linear trend for the association between both IGF-I and IGFBP-3 was evaluated by including categorical trend variables in the regression model. Effect modification was evaluated by stratified analysis and by inclusion of the cross-product term between the factor of interest and serum IGF-I or IGFBP-3 as a continuous term into the logistic regression models. For the SSS, mean change in serum IGF-I and IGFBP-3 over time according to case status was evaluated using a paired t test analysis (cases were pair matched to controls on age, intervention

assignment, and time between blood draw). All of the statistical analyses were conducted using the Statistical Analysis System (SAS, Cary, NC).

RESULTS

Selected characteristics of the prostate cancer cases and controls included in the RAS analysis are presented in Table 1. Cases and controls were generally comparable except for age at baseline and years of smoking (these factors are highly correlated, $r = 0.60$). Serum IGF-I and IGFBP-3 were correlated among both cases and controls ($r = 0.70$; $P < 0.001$). Age was not correlated with either IGF-I or IGFBP-3 among both the cases and the controls. There were no differences in mean serum concentrations of IGF-I or IGFBP-3 by case status (Table 1). In addition, there were no significant differences according to disease stage or grade (data not shown).

The associations between serum IGF-I and IGFBP-3 and prostate cancer risk are shown in Table 2. We found no significant association between prostate cancer risk and either serum IGF-I (OR, 0.52; 95% CI, 0.23–1.16 after adjusting for age, BMI, intervention group assignment, and serum IGFBP-3 level) or serum IGFBP-3 (OR, 1.93; 95% CI, 0.83–4.49 after adjusting for age, BMI, intervention group assignment, and serum IGF-I level). When we examined the ratio of IGF-I:IGFBP-3 we observed a borderline significant inverse association (Table 2). To determine whether either serum IGF-I or IGFBP-3 was associated with more advanced disease, we evaluated their associations with prostate cancer risk stratified by cancer stage at diagnosis (stage 0-II *versus* III-IV). There were essentially no differences in the associations according to disease stage. Furthermore, we found no significant interactions between serum IGF-I or IGFBP-3 and BMI, height, smoking, or intervention group. Because previous studies showed an interaction of serum IGF-I with age (8, 9, 12), we evaluated whether age modified the associations between IGF-I and IGFBP-3 and prostate cancer risk, and found no age interaction with either IGF-I ($P = 0.93$) or IGFBP-3 ($P = 0.09$).

Table 3 presents serum levels of IGF-I and IGFBP-3 for cases and controls in the SSS sample. Follow-up time between case diagnosis blood draw and previous blood draw averaged 3 years for both cases and their matched controls. The mean was 61 years for both cases and controls. There was a significant difference in the change in serum IGF-I over time between cases and controls. The cases had an average 18% increase in serum IGF-I levels compared with a 4% decrease among controls ($P = 0.02$). Interestingly, the serum IGF-I increase observed in the cases was associated with stage of disease at diagnosis. The largest case-control differences in the change in serum IGF-I between blood collections was seen in those men with advanced stage disease (*i.e.*, stage III-IV cases had a 29% increase in serum IGF-I,

Table 1 Baseline characteristics according to prostate cancer case, ATBC Study, Finnish

	Mean (SD)		P^a
	Cases ($n = 100$)	Controls ($n = 400$)	
Age at baseline, year	59.0 (4.6)	56.4 (5.0)	<0.01
Age at diagnosis, year	68.6 (4.6)	—	—
Height, cm	174.4 (5.9)	173.8 (6.0)	0.39
Weight, kg	80.8 (14.9)	80.5 (13.2)	0.96
BMI	26.5 (4.5)	26.6 (3.9)	0.53
Energy intake (kcal/day) ^b	2831.5 (736.3)	2834.4 (821.6)	0.91
No. cigarettes smoked daily	20.9 (9.0)	20.5 (8.4)	0.83
Years of cigarette smoking	37.5 (8.1)	34.8 (8.5)	<0.01
Alcohol intake (g/day)	17.3 (23.4)	19.6 (23.5)	0.42
IGF-I (ng/ml)	146.5 (52.5)	146.7 (50.9)	0.41
IGFBP-3 (ng/ml)	2502.0 (746.3)	2398.6 (635.8)	0.17

^a P s based on Wilcoxon rank sums test, and all P s are two-sided.

^b BMI = weight in kg/(height in meters)².

Table 2 Risk of prostate cancer according to quartile of IGF-I, IGFBP-3, and IGF-I:IGFBP-3 ratio in the ATBC study, cases diagnosed 5–12 years after blood draw

	Quartile				P for trend ^a
	1	2	3	4	
IGF-I					
Median, ng/ml (range)	65.4 (3.9–87.3)	104.8 (87.6–121.6)	141.5 (121.8–167.4)	210.2 (167.5–395.7)	
OR (95% CI) ^b	1.00 (referent)	0.61 (0.32–1.18)	0.90 (0.48–1.67)	1.00 (0.54–1.87)	0.74
OR (95% CI) ^c	1.00 (referent)	0.50 (0.26–0.98)	0.59 (0.29–1.20)	0.52 (0.23–1.16)	0.16
No. of cases	29	20	25	26	
No. of controls	95	106	100	99	
IGFBP-3					
Median, ng/mL (range)	2156 (236–2620)	3084 (2622–3602)	4135 (3606–4859)	5805 (4875–9850)	
OR (95% CI) ^b	1.00 (referent)	1.49 (0.79–2.81)	1.28 (0.68–2.42)	0.71 (0.36–1.39)	0.10
OR (95% CI) ^d	1.00 (referent)	0.78 (0.39–1.56)	1.51 (0.73–3.12)	1.93 (0.83–4.49)	0.06
No. of cases	26	19	26	29	
No. of controls	99	106	99	96	
IGF-I:IGFBP-3 ratio					
Median, ng/ml (range)	.045 (.021–.050)	.056 (.050–.060)	.063 (.060–.070)	.077 (.070–.13)	
OR (95% CI) ^b	1.00 (referent)	0.52 (0.28–0.98)	0.54 (0.29–1.02)	0.54 (0.29–1.01)	0.06
No. of cases	33	23	22	22	
No. of controls	92	102	103	103	

^a P for trend based on quartile trend variable and all Ps are two-sided.

^b OR and 95% CI after adjusting for age, BMI, and intervention group assignment.

^c OR and 95% CI after adjusting for age, BMI, intervention group assignment and IGFBP-3.

^d OR and 95% CI after adjusting for age, BMI, intervention group assignment, and IGF-I.

and their matched controls had a 9% decrease in IGF-I over time; $P = 0.10$). In contrast to the IGF-I findings, changes in serum IGFBP-3 levels over time did not differ significantly by case-control status in the SSS ($P = 0.29$). Changes in serum PSA, a marker associated with disease stage, paralleled increases in serum IGF-I over time, suggesting that increased tumor volume may have contributed to changes in serum factors (serum PSA increased by 200% in the cases and 26% among the matched controls; $P = 0.007$).

DISCUSSION

The RAS analysis of this study was designed to evaluate the etiologic role of IGF-I and IGFBP-3 in the development of prostate cancer by exploring the relationship among prostate cancer cases who were diagnosed, on average, 9 years after blood collection. As such, in this nested case-control study within a large cancer prevention trial, the ATBC Study, we found no prospective association between serum IGF-I or serum IGFBP-3 levels and prostate cancer risk. In fact, contrary to the hypothesized increase risk associated with IGF-I, we observed a decrease in risk associated with IGF-I after adjusting for IGFBP-3 (including IGFBP-3 in the model or evaluating the IGF-I:IGFBP-3 ratio).

These findings contrast with an earlier report from a prospective study of United States men with an average of 5 years of follow-up that showed a 4-fold increase in prostate cancer risk in high *versus* low quartile of serum IGF-I (8). A prospective study of Swedish men

with up to 10 years of follow-up showed no overall association between prostate cancer risk and serum IGF-I, but a 4-fold risk increase was observed for high *versus* low tertile among men who were ≤ 59 years old at study entry (9). Another prospective analysis of United States men showed no association between IGF-I or IGFBP-3 and prostate cancer (10). Of three incident case-control studies, two found significant positive associations between serum IGF-I and prostate cancer, whereas the third found no overall association, but did observe a significantly increased risk for elevated serum IGF-I in younger men (12). Two studies reported inverse associations between IGFBP-3 and prostate cancer, none of which reached statistical significance, however (8, 13).

In our analysis, age did not modify the association between IGF-I and prostate cancer risk. Previous published data regarding age interactions have been inconsistent. Chan *et al.* (8) observed a much stronger effect among older men in the presence of a significant main effect of IGF-I. On the other hand, two studies (9, 12) observed no main effects of IGF-I but a 2–3-fold increased risk associated with IGF-I only among younger men. Because men who are diagnosed with cancer at a younger age are generally found to have more aggressive disease, we evaluated these associations after stratifying by baseline age, age of cancer diagnosis, tumor stage, and tumor grade and found no effect modification by any of these parameters on the associations between IGF-I or IGFBP-3 and prostate cancer risk.

The fact that all of the participants in the present analysis were long-term smokers (*i.e.*, average 20 cigarettes daily for 36 years) enrolled in a lung cancer prevention study may also account for some of the differences in comparison with other studies that contained many nonsmokers. This is supported by the fact that associations between cigarette smoking, and IGF-I and IGFBP-3 levels have been reported (positive and negative, respectively; Refs. 16, 17), and that measurement of IGFs in smokers may not adequately reflect chronic IGF exposure status. However, serum IGF-I and IGFBP-3 were not related to smoking intensity or duration in our study. In addition, in the prospective study of Swedish men, no association was observed between smoking status (*i.e.*, current, former, *versus* nonsmoker) and IGF-I or IGFBP-3 serum levels, and smoking status did not modify the IGF-prostate cancer association (9).

It is possible that the positive association between serum IGF-I and prostate cancer risk observed by some investigators may have resulted from an effect of preclinical disease on serum levels of IGF-I. This

Table 3 Serum IGF-I and IGFBP-3 of cases (from cancer diagnosis to and from 2–5 years before diagnosis) and matched controls, ATBC Study, Finnish men

	Serum factor Mean (SD)		P ^b
	Cases (n = 21)	Controls (n = 21) ^a	
Serum IGF-I (ng/ml)			
At time of diagnosis	86.4 (30.2)	79.0 (23.0)	
>2 years before (or control visit) ^c	73.1 (23.2)	82.1 (20.6)	
Difference	+18%	–4%	0.02
Serum IGFBP-3 (ng/ml)			
At time of diagnosis	2067.7 (474.0)	2144.3 (656.3)	
>2 years before dx (or control visit)	2033.2 (521.8)	2240.5 (531.1)	
Difference	+1.7%	–4.3%	0.29

^a Controls matched to cases on age, intervention assignment, and time between 2 blood draws.

^b P was based on the matched paired *t* test.

^c For controls median time = 3.04 and cases = 3.03 years.

would suggest that serum IGF-I may serve as a tumor marker (*e.g.*, the tumor is secreting IGF-I) rather than an etiologic role in the development of prostate cancer. Although the two prior prospective studies attempted to eliminate this bias by excluding men with <5 years between blood draw and diagnosis, it is unclear whether 5 years is enough time to diminish the effect of preclinical disease. In the study by Stattin *et al.* (9), 80% of the cases had elevated PSA levels at baseline, and Chan *et al.* (8) showed a much stronger association between IGF-I and prostate cancer risk among men who had PSA >4 ng/ml at baseline (a potential correlate of more advanced disease). This implies that the cases in these two prior prospective studies may have had disease even at the time of the baseline blood collection.

We were able to additionally elucidate the influence of the presence of tumor on serum IGF-I in the SSS by analyzing the changes in serum IGF-I from time of diagnosis to up to 2–5 years before diagnosis in serial samples among prostate cancer cases and matched controls in the ATBC cohort. Our data support the hypothesis that serum IGF-I may be serving as a tumor marker. Although serum IGFBP-3 levels did not change, we observed a statistically significant 18% increase in serum IGF-I level over 3 years in cases compared with a 4% decrease in controls. Our finding that serum PSA, a measure associated with disease stage, increased in parallel to IGF-I lends additional support to this hypothesis. The largest increase in serum IGF-I was observed in those patients with advanced stage disease, which has been supported by another large prospective study (18), showing an association between serum IGF-I and advanced stage disease but not early stage disease. One possible explanation for this is that local production and secretion of IGF-I from the increased tumor volume associated with advanced disease contributes to the observed elevation in serum IGF-I.

There are several explanations for a possible influence of the presence of tumor on circulating levels of growth factors. For instance, circulating levels may be influenced by tumor growth as a result of altered expression of growth factors in tumor tissue. Tumors may also elicit an endocrine response, as has been demonstrated experimentally. In a mouse model, the induction of tumors by either a chemical (MCA) or oncogenic virus (MMTV) resulted in a reduction in blood levels of insulin and prolactin (19). Interestingly, Kaplan *et al.* (20) observed a significant increase of serum IGF-I with increasing tumor burden in a transgenic mouse model of prostate cancer. However, in a cross-sectional study, there was no relationship between blood IGF-I levels and prostate cancer pathologic parameters in patients (21).

In conclusion, in contrast to previous studies, we found no evidence of an association between either serum IGF-I or IGFBP-3 in prospectively collected serum and prostate cancer risk in Finnish male smokers. The present study with its more detailed consideration of time before diagnosis suggests that serum IGF-I may serve as a tumor marker rather than an etiologic factor in prostate cancer. This finding needs confirmation in larger study populations before conclusions can be drawn regarding the precise role of IGF-I in this disease.

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