

SERUM COMPONENTS AND RISK OF CANCER - III

Prostate Cancer Risk in Relation to Insulin-like Growth Factor (IGF)-I and IGF-Binding Protein-3: A Nested Case-Control Study in Large Scale Cohort Study in Japan (JACC Study)

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Abstract

High levels of insulin-like growth factor (IGF)-I are reported to be associated with an increased risk of prostate cancer. On the other hand, the insulin-like growth factor binding protein-3 (IGFBP-3) may decrease the risk. We therefore investigated the influence of serum IGF-I and IGFBP-3 on prostate cancer risk in a case-control study nested within a large-scale cohort in Japan (the Japan Collaborative Cohort Study). Information on lifestyles and sera of the subjects were collected in 1988-90. Serum IGF-I, IGF-II and IGFBP-3 were measured in sera stored at -80°C by immuno-radiometric assay. In 13,508 male subjects of the cohort who donated sera, 40 cases and 120 controls (1:3 matched with age and survey area) were identified. Ages of the cases ranged from 59 to 79 years, with a mean of 69.8. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the highest and middle tertiles compared with the lowest in controls using a conditional logistic model. Non-adjusted ORs for the highest tertiles were 0.99 (95% CI, 0.34-2.91) for IGF-I (trend-P = 0.60), 1.91 (95% CI, 0.68-5.38) for IGFBP-3 (trend-P = 0.23), 1.73 (95% CI, 0.69-3.47) for IGF-II (trend-P = 0.23), and 0.67 (95% CI, 0.26-1.76) for the IGF-I/IGFBP-3 ratio (trend-P = 0.83). Serum levels of IGF-I, IGF-II, IGFBP-3, or IGF-I/IGFBP-3 ratio were thus not thought to be associated with risk of prostate cancer.

Keywords: Japan Collaborative Cohort Study - nested case-control study - prostate cancer - IGF system

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Introduction

Incidence and mortality rates of prostate cancer are much lower among Japanese men compared with Western populations. However, both have rapidly increased recently (Editorial Board of Cancer Statistics in Japan, 2003). In Japan, little is known about prostate cancer epidemiology as compared with Western countries (Hirayama et al., 1979; Mishina et al., 1985; Ohno et al., 1988; Sonoda et al., 2004; Ozasa et al., 2004).

High levels of insulin-like growth factor (IGF)-I are reported to be associated with increased risk of prostate

cancer (Chan et al., 1998; Stattin et al., 2000; Chokkalingam et al., 2001; Renehan, 2004; Allen, 2007; Roddam, 2008). In contrast, there is evidence that IGF-binding protein-3 (IGFBP-3) decreases the risk (Chokkalingam et al., 2001; Roddam, 2008; Chen et al., 2005). However, recently many studies have found no association between IGF-I or IGFBP-3 and prostate cancer (Lacey et al., 2001; Severi et al., 2006; Borugian et al., 2008). We therefore here investigated serum IGF-I, IGF-II and IGFBP-3 as possible risk factors for prostate cancer in a case-control study nested in a large-scale cohort in Japan (the Japan Collaborative Cohort Study).

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Materials and Methods

As part of the Japan Collaborative Cohort Study (JACC Study), we carried out a nested case-control study. The study involved 46,465 males who were 40 to 79 years of age at baseline survey with self-administered questionnaire (1988-1990) from 45 areas all over Japan (Ohno et al., 2001; Tamakoshi et al., 2005).

Blood samples were collected in 37 out of 45 areas during the same period as the questionnaire survey. Eventually, 14,105 men (29.3% of the respondents to the questionnaire survey) provided blood samples. Sera were separated from the samples at laboratories in or near the municipalities. The serum derived from each participant's sample was divided into three to five tubes (0.1-0.5 ml per tube), which were stored in deep freezers at -80°C until analyzed. The stability of frozen serum levels was already confirmed (Ito et al., 2005). The study design and use of serum were approved by the Ethical Board at the Nagoya University School of Medicine, where the central office of the JACC Study was located at the time.

With respect to death from prostate cancer, survival

Table 1. Characteristics of the Prostate Cancer Cases and Controls

	Cases		Controls		P value
Age (y)*	69.3	(5.7)	69.1	(5.5)	0.51
BMI (kg/m ²)*	22.16	(2.87)	22.46	(2.67)	0.55
IGF-I (ng/ml)	120.76	(64.92)	120.04	(58.87)	0.95
IGFBP-3 (µg/ml)	2.95	(0.92)	2.84	(0.91)	0.52

Mean (SD) values; *at the baseline survey; BMI, body mass index

Table 2. Age-adjusted ORs for Prostate Cancer Risk with Reference to BMI Tertiles

Category	N	OR	95% CI	Trend P
Tertile 1*	58	1		0.44
Tertile 2	50	0.74	0.24-2.30	0.61
Tertile 3	48	0.65	0.21-1.95	0.44

*Tertiles among control subjects used as the cutoffs (in ng/mL): tertile 1, <21.3; tertile 2, 21.3 to 23.8; and tertile 3, >23.8. The first (lowest) tertile is the reference category

Table 3. ORs for Prostate Cancer Risk with Reference to IGF-I/II and IGFBP-3 (non-adjusted and adjusted for body mass index)

Items	Category	N	Crude			Adjusted for body mass index		
			OR	95% CI	Trend P	OR	95% CI	Trend P
IGF-I	Tertile 1*	56	1		0.60	1		0.61
	Tertile 2	33	0.26	0.08- 0.86	0.03	0.24	0.07- 0.84	0.03
	Tertile 3	71	0.99	0.34- 2.91	0.99	1.10	0.35- 3.47	0.87
IGF-II	Tertile 1	53	1		0.23	1		0.16
	Tertile 2	54	1.21	0.45-3.27	0.70	1.25	0.46-3.38	0.67
	Tertile 3	53	1.73	0.69-3.47	0.24	1.95	0.75-5.04	0.17
IGFBP-3	Tertile 1	49	1		0.23	1		0.17
	Tertile 2	55	1.25	0.51- 3.08	0.63	1.24	0.49- 3.13	0.65
	Tertile 3	56	1.91	0.68- 5.38	0.22	2.27	0.74- 6.93	0.15
IGF-I/IGFBP3	Tertile 1	56	1		0.83	1		0.78
	Tertile 2	52	0.65	0.23-1.83	0.41	0.63	0.22-1.84	0.40
	Tertile 3	52	0.67	0.26-1.76	0.42	0.60	0.22-1.61	0.31

*Levels of tertiles were <99 for tertile 1, 99 to 130 for tertile 2, and >130 for tertile 3 for IGF-I (ng/mL), <510, 510-600, and >600 for IGF-II (ng/mL), <2.37, 2.37 to 3.03, and >3.03 for IGFBP-3 (ng/mL), and <37.2, 37.2 to 49.8, and >49.8 for the IGF-I/IGFBP-3 ratio

was initially investigated in resident registration books in the municipalities, and the cause of death was confirmed in death certificates. With respect to incidence, we investigated the cancer registries in 24 study areas out of 45. We defined prostate cancer as the code C61 in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The subjects were followed up until the end of 1997 for death and until the end of 1994 for incidence. Residents who reported having had prostate cancer in the baseline survey were out of the objects.

There were 25 dead cases of prostate cancer and 15 incident cases. These 40 cases were included in this study. We analyzed incident and dead cases together in order to maximize sample size for analysis. The mean time plus minus SD from the baseline survey to the diagnosis or death due to prostate cancer was 5.3±2.4 years. Three controls for each case were randomly selected from the subjects without death or any cancer incidence by matching for study area and age (within 3 years). The control group was comprised of 120 males.

All serum samples were assayed at a single laboratory (SRL, Hachioji) in 2002. Laboratory staff used immunoradiometric assay to measure the concentration of serum IGF-I, IGF-II, and IGFBP-3, blinded to case-control status. Serum values were then divided into tertiles, based on the distribution of serum value in the controls. The first tertile was used as the reference category. Analysis of the odds ratio (OR) and 95% confidence interval (CI) for IGF-I, IGF-II, IGFBP-3 and the IGF-I/IGFBP-3 ratio was carried out using matched pair case-control methods and the PHREG procedure in the Statistical Analysis System (SAS) package. ORs were stratified for body mass index (BMI) and the survey area.

Results

Forty cases and 120 controls were enrolled. Characteristics of these cases and controls are shown in Table 1. Age and BMI levels at baseline survey were similar between cases and controls. Also, the serum concentrations of IGF-I, IGF-II, and IGFBP-3 were

similar between them. Table 2 shows the ORs of prostate cancer for BMI, no association with prostate cancer development being observed.

Table 3 shows the ORs for prostate cancer with reference to serum IGFs. The serum IGF-I level showed a significantly low OR in the middle tertile compared with the lowest tertile (OR, 0.26; 95% CI, 0.08-0.86), but this was not dose-dependent (trend $p=0.60$). The serum IGF-II level showed slight positive association with prostate cancer risk, but again this was not statistically significant (OR= 1.73 for the highest tertile, trend $p=0.23$). The serum IGF-BP-3 also showed slightly positive association with prostate cancer risk, but without statistical significance (OR= 1.91 for the highest tertile, trend- $p=0.23$). The ratio of serum IGF-I/IGFBP-3 was also not associated with prostate cancer risk. The ORs adjusted for BMI showed similar findings, although the association was slightly stronger for serum IGF-BP-3 when adjusted.

Discussion

IGF-I and IGF-II are polypeptides similar to insulin and regulate cell proliferation, differentiation and apoptosis in almost all sites in the human body, including the prostate. IGF-I is mainly secreted from liver and this is dependent on growth hormones. Circulating levels of IGF-I is affected age, sex and status of nutrition. On the other hand, IGF-II is thought to be a growth factor for early development. IGFBPs are their binding proteins and regulate IGF-I and IGF-II. Currently, there are 6 characterized IGF Binding Proteins (IGFBP1-6). IGFBP-3 is the major circulating IGFBP.

IGFs are thought to also play important roles in tumorigenesis. Relationships between IGFs and prostate cancer, postmenopausal breast cancer (Hankinson et al., 1998), colorectal cancer (Ma et al., 1999) and lung cancer (Yu et al., 1999; Wakai et al., 2002) have been suggested. Early studies (Chan et al., 1998; Stattin et al., 2000; Chokkalingam et al., 2001) and two meta-analyses (Renahan et al., 2004; Roddam et al., 2008) reported high levels of IGF-I to be a positive risk for prostate cancer. In contrast, high levels of IGFBP-3 are reported to have a negative risk (Chokkalingam et al., 2001; Roddam et al., 2008; Chen et al., 2005). However, the results have been inconsistent.

One recent meta-analysis including both prospective and retrospective studies ($n=7,481$ for IGF-I and $6,541$ for IGFBP-3) found an increased risk associated with the highest compared to the lowest quartile of IGF-I (OR=1.21, 95% CI: 1.07, 1.36), and a decreased risk for IGFBP-3 (OR=0.88, 95% CI: 0.79, 0.98) (Rowlands et al., 2009). However, -among studies about IGFBP-3, a sensitivity analysis excluding one study which was extreme outlier with a much lower OR compared with the other studies (OR=0.07, 95% CI 0.04, 0.12) resulted in a pooled OR of 0.95 (95% CI: 0.89, 1.02). The result for IGFBP-3 was thus equivocal. No association of IGF-II with prostate cancer was evident with the same meta-analysis. The IGF-I/IGFBP-3 ratio can be used to estimate the proportion of free IGF-I in the circulation. However, it also showed null association. The meta-analysis thus

only showed that a raised circulating IGF-I was positively associated with prostate cancer.

They also found that retrospective study designs provided consistently stronger associations than prospective studies; for example, for IGF-I, the pooled OR was 1.26 (1.05, 1.52) from retrospective studies compared to a pooled OR of 1.07 (0.97, 1.18) from prospective studies. Statistically the difference comparing retrospective with prospective study designs for IGF-I or IGFBP-3 was not significant, however. Concerning stage and grade of prostate cancer, IGF-I showed generally stronger associations with more aggressive (OR = 1.21, 95% CI 0.97 - 1.51) and advanced (OR = 1.41, 95% CI 1.07 - 1.85) cancers, compared to nonaggressive (OR = 1.05, 95% CI 0.99 - 1.12) and localized (OR = 1.10, 95% CI 0.98 - 1.22) lesions, but the statistical evidence for differences was weak. A similar but opposite pattern was seen for IGFBP-3. These findings suggested that the IGF system is associated with clinical progression of prostate cancer

In Asian countries including Japan, there have been few epidemiological studies about relationship between IGFs and prostate cancer. A case-control study with 128 prostate cancer cases in China (Chokkalingam et al., 2001) revealed that men in the highest quartile of the IGF-I levels had a 2.6-fold higher prostate cancer risk compared with the lowest quartile, with a significant trend (OR= 2.63; 95% CI= 1.19 - 5.79; trend $P = 0.01$). In contrast, men in the highest quartile of IGFBP-3 levels had a 46% decreased risk relative to the lowest quartile (OR = 0.54; 95% CI = 0.26 -1.15; trend $P = 0.08$).

In Japan, measurement of circulating IGF-I and IGFBP-3 levels was performed for 112 patients with prostate cancer and 32 patients with benign prostate hyperplasia (Miyata et al., 2003). Serum IGF-I levels in advanced prostate cancer patients were significantly higher than in BPH patients. In addition, IGFBP-3 levels in advanced prostate cancer patients were significantly lower than in localized prostate cancer or BPH patients. Unfortunately, the authors did not show any relationship between IGFs and prostate cancer incidence.

To our knowledge our study is the first report concerning association between IGFs and prostate cancer in Japan. We did not show any significant association between IGF-I and prostate cancer, although IGF-II and IGFBP-3 showed weak associations. Our results for IGF-I therefore differ from those of the recent meta-analyses (Roddam et al., 2008; Rowlands et al., 2009).

Circulating IGF-I levels are considered to be related to total calorie intake (Wolk, 2005). Food deprivation leads within a few days to strong reduction in circulating IGF-I levels, and chronic energy malnutrition is also associated with reduced levels (Thissen et al., 1994; Clemmons et al., 1991; Kaaks et al., 2001). Dossus and Kaaks summarized that IGF-I synthesis also depends on the intake of essential amino acids from animal proteins besides energy balance (Dossus and Kaaks, 2008). In Japan, meat consumption was revealed to be a positive risk of prostate cancer in an early cohort study (Hirayama, 1979), similar to some studies in Western countries (Ma et al., 2009). However, the Japanese diet markedly differs

from those in Western countries. Total energy intake is lower (WHO Expert consultation, 2004), and the BMI is lower in Japan compared to Europe and the United States (Zhou et al., 2003). The average daily energy intake in American males was 2,478 kcal compared to 2,163 kcal in Japanese males in 2001 (WHO Expert consultation, 2004). Such a difference in dietary habits might have influenced the results of our study. However, a case-control study in China found a positive association between IGF-I and prostate cancer (Chokkalingam et al., 2001), although the study design was different. So, there may be another reason for the lack of a definite relationship in our study. For example, the small number of 40 cases might have exerted an influence. Another possibility is that a selection bias was present in our study, because only about 30% of male subjects provided blood samples, and blood samples were mainly collected at health screening.

We could not evaluate the association between IGFs and stage or pathological grade of prostate cancer. Our study did not obtain data for PSA at diagnosis, TNM stage and pathological grade, because the cancer registry data available to us were occasionally incomplete and data for PSA were not included.

In conclusion, this first study concerning associations between the IGF system and prostate cancer risk in Japan did not reveal any significant consistent links with serum IGF-I, IGF-II, IGFBP-3, or the IGF-I/IGFBP-3 ratio.

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