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Correlation of Serum Insulin-like Growth Factor 1 with Prostate Cancer

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Abstract

Background: Insulin-like growth factor-1 can act in both an autocrine and paracrine manner to promote normal growth and malignant cellular proliferation. The importance of this factor as a major regulatory peptide has been established for cells, in vitro and in vivo. However, the role of serum insulin-like growth factor-1 levels in the etiology of benign prostatic hyperplasia and prostate cancer has not received sufficient attention. The aim of this study was to determine the relationship between benign prostatic hyperplasia, prostate cancer, and serum insulin-like growth factor-1 levels.

Methods: We collected blood samples from 68 individuals with prostate cancer (cases) and 68 individuals with benign prostatic hyperplasia (controls) who were patients at Imam Khomeini Hospital in Tehran, Iran. Those with benign prostatic hyperplasia had normal prostatic specific antigen levels <4 ng/ml and normal prostate according to digital rectal examination. The case group was selected from patients with pathologically confirmed prostate cancer. Insulin-like growth factor-1 concentrations were measured by a radio immunoassay kit. We used the t-test to compare insulin-like growth factor-1 levels between groups.

Results: Patients in the prostate cancer group had a mean age of 68 years, whereas those with benign prostatic hyperplasia had a mean age of 65 years (P>0.05). Mean serum insulin-like growth factor-1 levels were 219 ng/ml for the case group and 133 ng/ml for the control group, which was significant (P=0.0009). We did not observe any correlation between age and insulin-like growth factor-1 in the case group (P=0.83, r= -0.47), however there was a significant correlation in the control group (P=0.007, r=0.549). Although correlation between prostate volume and serum insulin-like growth factor-1 levels was not statistically significant in the case group (P=0.38, r=0.213), there was a positive correlation observed in the control group (P<0.008, r=0.537).

Conclusion: Our findings suggest that insulin-like growth factor-1 may have an etiologic role in prostate cancer. This interpretation is strengthened by the significant difference observed between serum insulin-like growth factor-1 levels in benign prostatic hyperplasia and prostate cancer patients. These results also offer additional opportunities for evaluating patients who have abnormal digital rectal exams or prostate specific antigen levels, yet their biopsies are normal. Under these circumstances, measurement of serum insulin-like growth factor-1 may assist with the decision for a second biopsy.

Keywords: Insulin-like growth factor, BPH, Prostate cancer

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Table 1. Data in prostate cancer and BPH groups*.

Demographics	Prostate cancer	BPH	*P*
Age (years)	68.09±6.1(53-81)§	65.47+9.49(50-82)	0.057
IGF-1 serum level(ng/ ml)	219.47±62.26(120-335)	133.08±61.9(47-281)	<0.001
PSA(ng/ ml)	16.49±8.52(40-65)	2.6±1.59(0.1-6)	<0.001
Prostate volume(cm^3)	39.94±8.97(25-60)	43±16.19(20-40)	0.175

*Values of continuous variables are shown as mean ±standard deviation; § Value in ( ) are min and max

Introduction

Although prostate cancer is the most common cancer amongst men, its etiologic factors have not been completely determined. Until recently the only recognized risk factors for prostate cancer were considered to be age, family history, race, and social status.[1] Multiple studies have demonstrated that increased serum levels of insulin-like growth factor-1 (IGF-1) positively correlate with prostate cancer risk.[2-4] Some studies have shown that IGF-1 plays an important role in breast and colorectal cancers.[5,6]

IGF-1 is mainly secreted by the liver in addition to several other tissues in response to growth hormones.[7] It has been documented that IGF-1 can act in an autocrine and paracrine manner to promote normal growth and malignant cellular proliferation. The importance of IGF-1 as a major growth regulatory peptide has been established for cells both in vitro and in vivo.[7-11] IGF-1 and its binding proteins are produced by normal prostate cells as well as prostate cancer cells and act locally through activation of IGF-1 receptors to stimulate cell proliferation.[12-15] However, the role of serum IGF-1 levels in the etiology of benign prostatic hyperplasia (BPH) and prostate cancer has not received sufficient attention.[16-19]

This was a case-control study to compare IGF-1 levels between prostate cancer and BPH.

Materials and Methods

We conducted this case-control study over a 24 month period (2009-2011). Blood samples were collected from 68 cases of histologically confirmed prostate cancer (case group) and 68 BPH cases as the control group at the Urology Clinic of Imam Khomeini Hospital in Tehran, Iran. All participants were well informed about the study and gave their consent to participate prior to having blood samples taken. We selected BPH cases from individuals over the age of 50 years who had normal prostate specific antigen (PSA; <4 ng/ml) levels and normal digital rectal examination (DRE) of the prostate. These patients visited the Urology Clinic with complaints of lower urinary tract symptoms. The case group was selected from patients with pathologically confirmed prostate cancer who referred to our center after their screening program. Cases were all above 50 years of age and had either an increased PSA level or abnormal DRE. Histological confirmation was performed by extended transrectal ultrasonography (TRUS) biopsy of the prostate, the results of which were reported by an expert pathologist. All patients who received any treatment for BPH or prostate cancer prior to blood collection were excluded from the study.

Clinical and demographic data were obtained as part of the tissue serum bank and database protocol. Patient's data that included name, code, age, family history of cancer and BPH, prostate volume, and PSA were recorded in a code sheet. Serum was extracted from blood samples and frozen at -20ºC until assayed. Laboratory personnel blinded to the case and control status analyzed the coded samples. IGF-1concentration was measured by a commercially available radio immunoassay kit (Diagnostic System Laboratories, Webster Texas). This highly sensitive, specific assay has no cross-reactivity to IGF-II and no interference from serum binding proteins. Intra- and inter-assay variation coefficients were less than 10%.

Serum IGF-1 levels were recorded on the code sheet as ng/ml. For statistical analysis, we used the independent samples t-test and Pearson's correlation coefficient in STATA 8.

Table 2. Correlation between IGF-1 levels in prostate cancer and BPH groups according to age, PSA, and prostate volume.

Variables	Prostatic cancer group		BPH group	
	r	*P*-value	r	*P*-value
Age	-0.47	0.831	-0.549	0.007*
PSA	0.421	0.051	0.193	0.377
Prostate volume	0.213	0.38	0.537	0.008*

*Significant at< 0.05.

Results

Mean age in the case (prostate cancer) group was 68±6.1 (53-81) years, whereas it was 65±9.49 (50-82) years for the control group, which was not statistically significant.

The mean serum IGF-1 level in the case group was 219±62.26 ng/ml (120-355) and for the control group, it was 133±61.9 ng/ml (47-281). Coefficient of variation (CV) for IGF-1 was 0.284 for cases and 0.465 for controls. Serum IGF-1 levels in the case group were significantly higher than controls (P<0.001). Because PSA was a differentiating factor between the case and control groups, the mean PSA level in the case group (16.4 ng/ml) was significantly higher than the control group (2.6 ng/ml; P<0.001).

Mean prostate volume as measured by TRUS in the control group (43 ml) was slightly higher than observed in the case group (39.9 ml) but was not statistically significant (P=0.175). Table 1 shows data from the case and control groups.

We calculated the Pearson correlation coefficient to examine the relationships between serum IGF-1 with age, PSA and prostate volume, separately, in each group (Table 2). There was no statistically significant correlation between age and IGF-1 in the case group however there was a moderately significant negative correlation between these two items in the control group.

There was no statistically significant correlation between serum IGF-1 levels and PSA in both groups. The correlation between prostate volume and serum IGF-1 level was not statistically significant in the case group, however in the control group there was a positive moderate correlation between these two items. Therefore the change in prostate volume paralleled the IGF-1 level in the control group (Table 2).

Discussion

With respect to IGF-1, the evidence which implicates it in the etiology of prostate cancer has been derived primarily from in vitro studies and pathophysiological considerations.

Normal and malignant prostate cells produce IGF-1.[12-14] Prostate cells express IGF-1 receptors and are very sensitive to stimulation by IGF.[12,13] In addition, antisense RNA to the IGF-1 receptor suppresses tumor growth and prevents invasion by rat prostate cancer cells *in vivo*.[16]

Our findings suggest that IGF-1 may play a role in the etiology of prostate cancer. This interpretation is strengthened by significant differences between serum IGF-1 in BPH and prostate cancer patients. We have determined that serum IGF-1 levels were independent from age in the case group, however there was an inverse significant relation in the control group.

It is our understanding that there have not been any studies published which reported the relationship between IGF-1 and age in either prostate cancer or BPH.

None of our patients underwent any treatments prior to blood sampling for serum IGF-1, thus the change was not secondary to treatment. Our study supported that of Chokalingman[17] observations on the relation between IGF-1 and prostate cancer risk. However our control group was selected from BPH patients and not from randomly chosen men, thus omitting the effect of BPH as a confounding factor. It must be emphasized that BPH is present in the majority of older males, thus it is difficult to locate men who do not have BPH.

It is interesting that recent prospective cohort studies have also shown an association in increased risk of colon and breast cancers to elevated plasma IGF-1 levels. These findings

suggest that an elevation of plasma IGF-1 may be a common risk factor for various cancers.[5,6]

Our findings found no association between prostate volume (possible cancer volume) and IGF-1 levels in the case group. This was similar to the results obtained by Shariat et al.[20] who also found no association between serum IGF-1 levels and prostate cancer stages.

Our study has some limitations. This was a cross-sectional study and could not satisfy the time sequence criterion for a cohort study for causality. The present study has a relatively small sample size, thus statistical significance was not a guarantee that chance did not contribute to the generation of results.

Conclusion

In conclusion, the results of the present study raise the possibility that IGF-1 may play a role in prostate cancer but provides no evidence that this factor plays a role in the etiology of BPH. These findings offer additional opportunities for evaluating patients with abnormal DRE or PSA levels, yet have a normal biopsy. Under these circumstances, measurement of serum IGF-1 levels can assist with decision making for a second biopsy.

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References

1. Klein E A, Platz EA, Thompson IM. Epidemiology, Etiology, and Prevention of Prostate Cancer. In: Wein AJ, Kavoussi LR, editors. Campbell's urology, 10th ed. Philadelphia: Saunders, 2011:2704-25.
2. Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO. Insulin-like growth factor I in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer* 1997;76:1115-8.
3. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-I and prostate cancer risk: A prospective study. *Science* 1998;279:563-6.
4. Wolk A, Mantzoros CS, Andersson SO, Bergstrom R, Signorello LB, Lagiou P, et al. Insulin-like growth factor 1 and prostate cancer risk: A population based case-control study. *J Natl Cancer Inst* 1998;90:911-4.
5. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999;91:620-5.
6. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 1998;351:1393-6.
7. LeRoith D, Clemmons D, Nissley P, Rechler MM. Insulin-like growth factors in health and disease. *Ann Intern Med* 1992;116(10):854-62.
8. Daughaday WH. The possible autocrine/paracrine and endocrine roles of insulin-like growth factors of human tumors. *Endocrinology* 1990;127(1):1-4.
9. Goustin AS, Leof EB, Shipley GD, Moses HL. Growth factors and cancer. *Cancer Res* 1986;46(3):1015-29.
10. Webster NJG, Resnik JL, Reichart DB, Strauss B, Haas M, Seely BL. Repression of the insulin receptor promoter by the tumor suppressor gene product p53: A possible mechanism for receptor overexpression in breast cancer. *Cancer Res* 1996;56(12):2781-8.
11. Ezzat S, Melmed S. Clinical review: Are patients with acromegaly at increased risk for neoplasia? *J Clin Endocrinol Metab* 1991;72(2):245-9.
12. Cohen P, Peehl DM, Stamey TA, Wilson KF, Clemmons DR, Rosenfeld RG. Elevated levels of insulin-like growth factor-binding protein-2 in the serum of prostate cancer patients. *J Clin Endocrinol Metab* 1993;76(4):1031-5.
13. Pietrzkowski Z, Mulholland G, Gomella L, Jameson BA, Wernicke D, Baserga R. Inhibition of growth of prostatic cancer cell lines by peptide analogues of insulin-like growth factor 1. *Cancer Res* 1993;53(5):1102-6.
14. Kimura G, Kasuya J, Giannini S, Honda Y, Mohan S, Kawachi M, et al. Insulin-like growth factor (IGF) system components in human prostatic cancer cell-lines: LNCaP, DU145, and PC-3 cells. *Int J Urol* 1996;3(1):39-46.
15. Angelloz-Nicoud P, Binoux M. Autocrine regulation of cell proliferation by the insulin-like growth factor (IGF) and IGF binding protein-3 protease system in a human prostate carcinoma cell line (PC-3). *Endocrinology* 1995;136(12):5485-92.
16. Burfeind P, Chernicky CL, Rininsland F, Ilan J. Antisense RNA to the type I insulin-like growth factor receptor suppresses tumor growth and prevents invasion by rat prostate cancer cells *in vivo*. *Proc Natl Acad Sci USA* 1996;93(14):7263-8.
17. Chokkalingman AP, Gao YT, Deng J, Stanczyk FZ, Sesterhenn IA, Mostofi FK, et al. Insulin-like growth factors and risk of benign prostatic hyperplasia. *Prostate* 2002;52(2):98-105.
18. Allen NE, Key TJ, Appleby PN , Travis RC, Roddam

AW, Rinaldi S, et al. Serum insulin-like growth factor (IGF)-I and IGF-binding protein-3 concentrations and prostate cancer risk: Results from the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2007;16:1121-7.
19. Kojima S, Inahara M, Suzuki H, Ichikawa T, Furuya Y. Implications of insulin-like growth factor-I for prostate cancer therapies. *Int J Urol* 2009;16(2):161-7.
20. Shariat SF, Jose A. Karam, , Karakiewicz PI . New blood-based biomarkers for the diagnosis, staging and prognosis of prostate cancer. *BJU Int* 2008;101(6):675-83.