Rapid Communication

Increased Serum Insulin Associated With Increased Risk of Prostate Cancer Recurrence

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BACKGROUND. In the present study, we assessed the relationship of serum insulin levels and risk of recurrence in men with localized prostate cancer because of the relationship of insulin to the development of prostate cancer, and because insulin is a growth factor.
METHODS. Participants in our study were found through urology and radiation oncology clinics, and all eligible patients were asked to take part. All patients were asymptomatic and had been initially diagnosed on the basis of rising PSA or abnormal physical examination. Histological confirmation of diagnosis was obtained for all subjects. Serum insulin levels were determined by chemoluminescent assay with a standard, commercially available instrument (Immulite Diagnostic Products Corporation, Los Angeles, CA). Patients were divided into three risk groups: *Low risk*: serum PSA ≤ 10, stage $\leq$ T2a, or Gleason grade ≤ 6; *Medium risk*: serum PSA 10–15, Gleason 7 or stage $\leq$ T2b; *High risk*: Gleason >7, tumor in seminal vesicle biopsy, serum PSA >15 or stage T2c or T3.
RESULTS. Men, 112 in number, with prostate cancer were studied. There was a significant increase in serum insulin with risk group ($P = 0.002$, one-way ANOVA). Tukey's multiple range test showed that the insulin levels of high risk patients were significantly higher than the insulin levels of medium and low risk patients ($P = 0.05$) but the insulin levels of medium and low risk patients were not significantly different from one another.
CONCLUSIONS. Urologists are actively seeking additional biomarkers of prostate cancer aggressiveness. Many prostate cancers are quite indolent and may never cause a problem, but it is now impossible to identify such tumors with certainty. Further studies of serum insulin levels in prostate cancer as a biomarker might, therefore, be worthwhile. With more and better biomarkers, many older men might be spared the rigors of radiation therapy and/or surgery, and their complications. Also, new prostate cancer therapies might be directed toward inhibiting the mitogenic effects of insulin. *Prostate 50:1–3, 2002.* © 2002 Wiley-Liss, Inc.

KEY WORDS: **prostate cancer; insulin; growth factors; recurrence; treatment**

INTRODUCTION

PSA, Gleason score, and stage at diagnosis are currently the most reliable markers of prostate cancer prognosis and tumor aggressiveness [1]. But urologists are actively seeking additional biomarkers.

Many prostate cancers are quite indolent and may never cause a problem, but it is now impossible to identify such tumors with certainty. With more and better biomarkers, some older men might be spared the rigors of radiation therapy and/or surgery, and their complications.

Elevated insulin levels are associated with increased risk of prostate cancer [2]. Moreover, insulin is necessary for the growth of prostate cancer cells in

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culture. For example, a special serum-free defined medium that can support short-term, long-term, and clonal growth of the human prostatic carcinoma cell lines, LNCaP, DU 145, PC-3, and ALVA-31, must contain insulin [3].

In the present study, we measured insulin levels in a series of men with prostate cancer.

METHODS

Participants in our study were found through urology and radiation oncology clinics, and all eligible patients were asked to take part. All patients had been initially diagnosed on the basis of rising PSA or abnormal physical examination. Histological confirmation of diagnosis was obtained for all subjects. All participants gave informed consent. All staging was clinical, because almost all the patients were to receive I-125 seed implant.

We studied men referred for treatment of localized prostate cancer. In our treatment protocol, patients are divided into three risk groups [4].

Low Risk

Serum PSA ≤ 10, stage $\leq$ T2a, or Gleason grade ≤ 6. These patients are treated with a radioactive implant.

Medium Risk

Serum PSA 10–15, Gleason 7 or stage $\leq$ T2b. These patients are treated with three months of combined hormonal therapy followed by an implant.

High Risk

Gleason > 7, tumor in seminal vesicle biopsy, serum PSA > 15 or stage T2c or T3. These patients are treated with three months combined hormonal therapy, an implant, and after two months break 6,000 rads with external beam radiotherapy.

Serum insulin levels were determined by chemoluminescent assay with a standard, commercially available instrument (Immulite Diagnostic Products Corporation, Los Angeles, CA).

RESULTS

Patients, 112 in number, were studied. The youngest was 46 years old, the oldest was 88, average age was 67 ± 8.5 (mean $\pm$ SD). Patients, 52 in number, were low risk, 16 medium risk, and 44 high risk.

There was a significant increase in serum insulin with risk group ($P = 0.002$, one-way ANOVA; Fig. 1). Tukey's multiple range test showed that the insulin levels of high risk patients were significantly higher

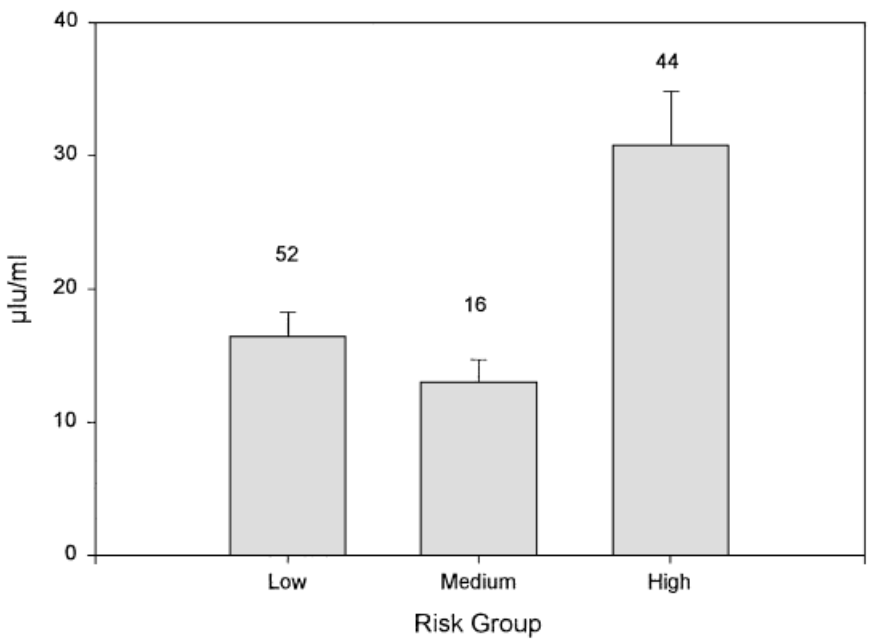

Fig. 1. Serum insulin (µIU/ml) levels of men with prostate cancer. Number of cases in each risk group above the error bar. There was significant variation of insulin ($P = 0.002$, one-way ANOVA). Tukey's multiple range test showed that the insulin levels of high risk patients were significantly higher than the insulin levels of medium and low risk patients ($P = 0.05$), but the insulin levels of medium and low risk patients were not significantly different from one another. (The upper limit of the normal range in our laboratory is 27 µIU/ml.)

than that of medium and low risk patients ($P = 0.05$), but the insulin levels of medium and low risk patients were not significantly different from one another.

DISCUSSION

Data from epidemiological and biological research implicate insulin-like growth factors I and II (IGF-I and IGF-II) in the regulation of prostate epithelial cell proliferation, and in the pathophysiology of prostate cancer [5]. But there has been little investigation into the role insulin itself plays in prostate cancer. Isolated epithelial cells of rat ventral prostate have insulin receptors, and fasting increases their concentration [6]. But PA-III rat prostate adenocarcinoma cells have no insulin receptor, though they do have specific binding sites for IGF-I and II [7].

One large epidemiologic study found an equivocal relationship between diabetes mellitus and prostate cancer. In hundreds of thousands of male respondents, the Cancer Prevention Study (1959–1972) explored whether men with diabetes were more likely to develop prostate cancer during a 13-year follow-up than were men without diabetes. After adjustment for factors associated with prostate cancer in previous studies, little association was found between diabetes at baseline and prostate cancer incidence. Men who had diabetes mellitus for 5 years or more, however, had a higher incidence of prostate cancer than did men without diabetes. But among all study participants who were diagnosed with prostate cancer, men with diabetes were only slightly more likely to die from prostate cancer than were men without diabetes [8].

The relationship between insulin level and risk group in prostate cancer we describe here is biologically quite plausible, since insulin is a growth factor. Further studies may document whether serum insulin level might be a useful biomarker of prostate cancer aggressiveness.

New prostate cancer therapies might be directed toward reducing insulin levels. For example, metformin is now used to restore normal menses in polycystic ovary syndrome by lowering serum insulin levels [9]. Metformin might prevent prostate tumor spread and recurrence in men with hyperinsulinemia by reducing insulin levels. Miglitol [10], indomethacin [11], troglitazone [12], and other insulin-lowering drugs could also potentially prevent recurrence.

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