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Association between serum triiodothyronine (t3) level and risk of disease recurrence in men with localized prostate cancer

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We assessed the relationship of serum triiodothyronine (t3) level and risk of disease recurrence in men treated for localized prostate cancer. 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 prostate specific antigen (PSA) or abnormal physical examination. Histological confirmation of diagnosis was obtained for all subjects. Serum (t3) level was determined by chemoluminescent assay with a standard, commercially available instrument (Immulite Diagnostic Products Corporation, Los Angeles, California). Sixty-eight men with prostate cancer were studied. In our treatment protocol, patients are divided into three risk groups: *low risk*: serum PSA ≤ 10, stage $\leq$ T2a, or Gleason grade ≤ 6. These patients are treated with a radioactive implant; *moderate risk*: serum PSA 10–15 or Gleason 7 or stage $\leq$ T2b. These patients are treated with 3 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 3 months combined hormonal therapy, an implant, and after 2 months break 6000 rad external beam radiotherapy. There was a significant increase in serum t3 with risk category $(P = 0.011)$. Tukey's multiple range B-test showed a significant difference between the t3 levels of the high risk patients, when compared to the t3 levels of the moderate $(P = 0.013)$ and low risk patients $(P = 0.041)$. The range test showed no significant difference between the t3 levels of the moderate and low risk patients $(P = 0.897)$. Because t3 levels may be affected by age, we performed multivariate linear regression, with t3 as the dependent variable. There was a statistically significant $(P = 0.035)$ association of t3 level with risk group, but there was no significant association of t3 with age $(P = 0.803)$. Multivariate linear regression, with t3 as dependent variable, PSA, Gleason score, and stage as independent variables showed a significant overall association of the three independent variables with t3 $(P = 0.042)$, though individually the relationships were not significant. None of the men had a t3 level that was above the normal range for our laboratory (137 ng/dl). 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 impossible to identify such tumors with certainty. Further studies of serum t3 level as a biomarker in prostate cancer

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might therefore be worthwhile. With more and better biomarkers, many older men might be spared the rigors of radiation therapy and/or surgery and the complications. Also, new prostate cancer therapies might be directed toward inhibiting the mitogenic effects of t3. *Prostate Cancer and Prostatic Diseases* (2001) 4, 232–234.

Keywords: prostate cancer; thyroid; triiodothyronine; stage; risk of recurrence

Introduction

Prostate specific antigen (PSA), Gleason score, and stage at diagnosis are currently the most reliable markers of prostate cancer prognosis and tumor aggressiveness.[1] Recently, visual estimate of the percentage of carcinoma was shown to be an independent predictor of prostate carcinoma recurrence after radical prostatectomy.[2] But urologists are actively seeking additional biomarkers. One such biomarker may be triiodothyronine (t3). Triiodothyronine is the active thyroid hormone, synthesized in the thyroid and produced by deiodination of a precursor, t4.

t3 is necessary for the growth of prostate cancer cells. 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 t3.[3]

There is a close relationship between prostate cancer and breast cancer. For example, familial clustering of breast and prostate cancers increases the risk of post-menopausal breast cancer.[4]

Normal and malignant breast cells are stimulated to grow by t3, a member of a family of growth factors. Because t3 plays an important role in the regulation of prostate and breast cell growth and differentiation,[5,6] we assessed the relationship of t3 levels and disease recurrence risk in men with localized prostate cancer.

Methods

Participants in our study were found through urology and radiation oncology clinics in 1999 and 2000. 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 and the study had Institutional Review Board approval. All staging was clinical, because the patients were to receive I-125 seed implant.

We studied 68 men referred for treatment of localized prostate cancer. In our treatment protocol, patients are divided into three risk groups, which were previously defined:[7] *low risk*: serum PSA ≤ 10, stage ≤ T2a, or Gleason grade ≤ 6. These patients are treated with a radioactive implant; *moderate risk*: serum PSA 10 – 15, Gleason 7 or stage ≤ T2b. These patients are treated with 3 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 3 months combined hormonal

therapy, an implant, and after 2 months break 6000 rad with external beam radiotherapy.

Serum for t3 was drawn prior to initiation of radiation therapy. Serum t3 level was determined by chemoluminescent assay with a standard, commercially available instrument (Abbott AxSYM, Abbott Laboratories, Abbott Park, Illinois, USA).

Results

The youngest patient was 46 y, the oldest 88 y, average age 67 ± 8.3 (mean ± s.d.). Twenty-four patients were low risk, 24 were moderate risk, and 20 were high risk. There was no significant difference in mean age in the three risk groups ($P = 0.446$).

There was a significant increase in serum t3 with risk category ($P = 0.011$, one way ANOVA, Figure 1). Tukey's multiple range B-test showed a significant difference between the t3 levels of the high risk patients, when compared to the t3 levels of the moderate ($P = 0.041$) and low risk patients ($P = 0.013$). The range test showed no significant difference between the t3 levels of the moderate and low risk patients ($P = 0.897$). Because t3
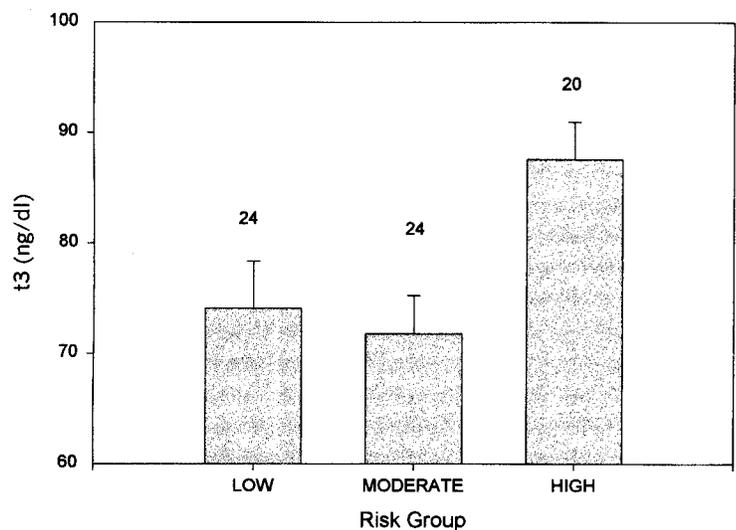

Figure 1 *Serum t3 (mean ± s.e.m.) levels in 68 prostate cancer patients, stratified by disease recurrence risk. Number of cases in each group is indicated above corresponding error bar. There is a significant increase in serum t3 with risk category ($P = 0.011$, one way ANOVA). Tukey's multiple range B-test showed a significant difference between the t3 levels of the high risk patients, when compared to the t3 levels of the moderate ($P = 0.014$) and low risk patients ($P = 0.041$). But the range test showed no significant difference between the t3 levels of the moderate and low risk patients ($P = 0.897$).*

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Table 1 Multivariate linear regression with t3 as dependent variable, risk group (low, moderate, high) and age as independent variables. There is a statistically significant ($P = 0.035$) association of t3 level with risk group, but no significant association of t3 with age ($P = 0.803$)

	B	s.e.	Standardized coefficients Beta	t	Sig.
(Constant)	58.06	19.815		2.93	0.005
Age	0.0753	0.300	0.034	0.251	0.803
Risk group	6.92	3.189	0.295	2.171	0.035

Table 2 Multivariate linear regression, with t3 as dependent variable, PSA, Gleason score, and stage as independent variables. There is a significant overall association of the three independent variables with t3 ($P = 0.042$), though individually the relationships are not significant

	B	s.e.	Standardized coefficients Beta	t	Sig.
(Constant)	45.966	13.696		3.356	0.001
PSA	0.3	0.33	0.119	0.909	0.367
Gleason	2.324	2.476	0.143	0.938	0.352
Stage	2.893	2.135	0.209	1.355	0.181
Dependent t3					

levels may be affected by age, we performed multivariate linear regression (Table 1), with t3 as the dependent variable. There was a statistically significant ($P = 0.035$) association of t3 level with risk group, but there was no significant association of t3 with age ($P = 0.803$).

Multivariate linear regression, with t3 as dependent variable, PSA, Gleason score, and stage as independent variables showed a significant overall association of the three independent variables with t3 ($P = 0.042$, Table 2), though individually the relationships were not significant. None of the men had a t3 level that was above the normal range for our laboratory (137 ng/dl).

Discussion

Epidemiologic studies have identified no definite relationship among t3, thyroid disease and prostate cancer. One study of localized and metastatic prostate cancer revealed no abnormality of t3.[8] Another study found a marginally decreased incidence of prostate cancer among men with myxedema.[9] Nevertheless, our finding of an association of serum t3 level with risk of disease recurrence in treated patients is not surprising, given the mitogenic potential of t3.

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 impossible to identify such tumors with certainty. Further studies of serum t3 level in larger numbers of prostate cancer patients might therefore be worthwhile, in order to eliminate the potentially confounding effects of stress or biopsy on serum t3. Also, a study directly correlating t3 and outcome should be done.

With more and better biomarkers, many older men might be spared the rigors of radiation therapy and/or surgery, and the complications. Also, new prostate cancer therapies might be directed toward inhibiting the mitogenic effects of t3.

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