

Occult Prostate Cancer in Men With Low Serum Testosterone Levels

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Objective.—To determine the prevalence of occult prostate cancer in men with low serum total testosterone or free testosterone levels.

Design.—Retrospective analysis of a consecutive series of men.

Setting.—Academic teaching hospital.

Patients.—Seventy-seven men with low total testosterone or free testosterone levels, with normal results of digital rectal examination and prostate-specific antigen (PSA) levels of 4.0 ng/mL or less. The mean age was 58 years.

Interventions.—Sextant prostate needle biopsies with ultrasound guidance.

Main Outcome Measures.—Results of prostate needle biopsies, transrectal ultrasound, prostate volume, PSA level, PSA density, total and free testosterone levels.

Results.—Prostate cancer was identified in 14% (11/77) of the entire group and in 10 men (29%) aged 60 years or older. The median age for men with cancer was 64 years. Histologic examination showed Gleason scores of 6 or 7 for all cancers. No significant differences were noted between the cancer and benign groups with regard to PSA level, PSA density, prostate volume, total testosterone level, or free testosterone level.

Conclusions.—A high prevalence of biopsy-detectable prostate cancer was identified in men with low total or free testosterone levels despite normal PSA levels and results of digital rectal examination. These data suggest that (1) digital rectal examination and PSA levels are insensitive indicators of prostate cancer in men with low total or free testosterone levels, and (2) PSA levels may be altered by naturally occurring reductions in serum androgen levels.

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A LOW SERUM testosterone level in men is associated with a number of medical conditions, most notably sexual dysfunction, and is commonly treated with exogenous testosterone supplementation. Since testosterone levels decrease as men age, a large number of men may be candidates for androgen replacement therapy.¹ However, with advancing age, men are also at increased risk of developing prostate cancer. One theoretical danger of testosterone therapy in hypogonadal men is stimulation of an occult prostate cancer into clinical disease.

Prostate cancer growth is stimulated in the presence of androgens and an-

drogen deprivation causes prompt regression of tumor volume.² Clinical reports have documented rapid clinical progression of unsuspected prostate cancer after testosterone administration.³

Because of concerns that testosterone replacement therapy may promote progression of occult carcinoma of the prostate among men at risk, we have added a step to the screening process for prostate cancer before testosterone treatment is initiated. In addition to proposed guidelines of normal results of digital rectal examination (DRE) and serum prostate-specific antigen (PSA) levels,⁴ we performed systematic prostate needle biopsies under transrectal ultrasound guidance. We hypothesized that low androgen levels may falsely lower PSA levels into the normal range and may alter the character of a prostate tumor so as to be undetectable by DRE.

Patients and Methods

From June 1991 to February 1996, 107 men referred for evaluation of sexual dysfunction were found to have low serum levels of total testosterone or free testosterone. These men were considered candidates for exogenous testosterone supplementation. Thirty of these men had either an abnormal result of DRE or PSA level, or were taking medication known to lower PSA level (finasteride) and were thus excluded from the study. The remaining 77 men had both normal PSA levels and results of DRE in association with low testosterone or free testosterone levels, and they composed the study group for this investigation.

Levels of testosterone and free testosterone were measured by radioimmunoassay (Diagnostic Products Corp, Los Angeles, Calif). Men were considered candidates for testosterone therapy, and thus candidates for inclusion in this study, on the basis of a single serum testosterone level less than 10.4 nmol/L (300 ng/dL) or a free testosterone level less than 0.06 nmol/L (1.6 ng/dL). Blood samples were obtained during clinical hours, ranging from 8 AM to 5 PM, and were repeated for borderline results because of the diurnal variation in testosterone levels. Serum PSA level was determined by the Abbott IMX kit (Abbott Laboratories, Abbott Park, Ill), which yields slightly lower values than the Hybritech assay (Hybritech Inc, San Diego, Calif).⁵ A PSA value of 4.0 ng/mL or less was considered normal.

Patients were screened for occult adenocarcinoma of the prostate with DRE, PSA, and transrectal ultrasound with transrectal ultrasound-guided prostate needle biopsy. The DRE was performed by a urologist. A normal DRE result was defined by the absence of nodularity, asymmetry, or unusual firmness of the prostate.

Transaxial and sagittal ultrasound scanning was performed by a staff ra-

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diologist with a 7.0-MHz end-fire transducer, and transrectal ultrasound-guided prostate needle biopsies were performed by a urologist with an automatic device (Biopsy, Bard Urological, Covington, Ga) by means of an 18-gauge needle. Systematic 6-sector core biopsy specimens were generally obtained, but quadrant biopsies were obtained for smaller prostates. Hypoechoic or otherwise suspicious areas noted by ultrasound also underwent biopsy.

Pathology specimens were reviewed by the clinical pathology staff at our institution. Carcinoma was graded according to the criteria of Gleason et al.⁶

Prostate volume was estimated by the prostate ellipse formula, in which volume equals $0.52 \times \text{length} \times \text{height} \times \text{width}$. The PSA density (PSAD) was determined by dividing serum PSA level by the calculated prostatic volume.

The nonparametric Mann-Whitney test was used for statistical comparisons of men with cancer and those without cancer, and the Fisher exact test was used to compare proportions of men in the cancer and benign groups with low testosterone levels.

Results

Characteristics of the 77 men included in the study are summarized in the Table. Since age has been shown to correlate with both prostate cancer incidence and PSA level, the group was divided into men younger than 60 years and those aged 60 years and older. The PSA values were similar for the younger and older subgroups (1.2 vs 1.5 ng/mL, respectively; $P=.12$), as were PSAD (0.036 vs 0.039; $P=.35$), prostate volume (32.2 vs 39.2 mL; $P=.12$), and free testosterone levels (0.041 vs 0.038 nmol/L [1.2 vs 1.1 ng/dL]; $P=.54$). The testosterone level was greater for the older group (13.9 vs 11.7 nmol/L [402 vs 336 ng/dL]; $P=.02$).

The results of transrectal ultrasound were normal for 70 men. Seven men had focal hypoechoic areas of the peripheral zone, and ultrasound-directed biopsies of these lesions were performed in addition to systematic biopsies. No cancer was found in the men with ultrasound abnormalities of the prostate.

Eleven men (14%) had adenocarcinoma of the prostate. All had total Gleason scores of 6 or 7. Five men had cancer in 1 of their biopsy samples; 2 men had cancer in 2 samples; 1 man had cancer in 3 samples; and 1 man had cancer in 5 samples. Two men had cancer in 1 sample together with high-grade prostatic intraepithelial neoplasia in additional samples. Six other men were found to have high-grade prostatic intraepithelial neoplasia without frank cancer.

The mean age of men with cancer was

Characteristics of Men With Benign and Malignant Histologic Findings on Prostate Biopsy*

Characteristics	Benign	Malignant	P
Age, mean (range), y	56.8 (36-70)	64.8 (52-81)	.001
PSA, mean (range), ng/mL	1.2 (0.2-3.9)	1.7 (0.4-3.7)	.15
PSAD, mean (range)	0.035 (0.009-0.134)	0.048 (0.012-0.100)	.05
Prostate volume, mean (range), mL	35.3 (15-83)	35.0 (14-64)	.87
Testosterone, mean (range), nmol/L [ng/dL]	12.3 (1.1-26.0) [356 (32-751)]	14.5 (8.6-20.1) [419 (249-580)]	.11
Free testosterone, mean (range), nmol/L [ng/dL]	0.04 (0.003-0.05) [1.1 (0.1-1.5)]	0.04 (0.02-0.05) [1.1 (0.7-1.4)]	.61
Testosterone/free testosterone, mean (range)	321 (148-548)	386 (269-522)	.02

*PSA indicates prostate-specific antigen; PSAD, PSA density (expressed as PSA level in nanograms per milliliter divided by calculated prostatic volume in milliliters).

higher than that of men with benign biopsy results (Table). No PSA level could be used as a diagnostic threshold, since a PSA level as low as 0.4 ng/mL was found in association with cancer.

Low total testosterone levels were present in 21 (32%) of 66 men with benign biopsy specimens compared with 2 (18%) of 11 men with cancer ($P=.73$), whereas all men in this study had low free testosterone levels (mean levels were nearly identical for both groups; Table). Interestingly, the ratio of testosterone/free testosterone level was higher for the cancer group than for the benign group.

All but 1 cancer (in a 52-year-old man) were diagnosed in men aged 60 years or older. The prevalence of cancer in this age group was 29%. Final pathologic classifications for the 6 men who underwent radical prostatectomy was T2a for 2 and T2b for 4. Additional pathologic findings were not available for the other men with cancer; 3 have been observed and 2 underwent primary radiation therapy.

Comment

The 14% prevalence of cancer in this population is greater than would be expected for a group with normal PSA levels and DRE results, suggesting that some men in this group might have demonstrated an elevated PSA level or abnormal DRE finding with full androgenic stimulation. Also, the data suggest that use of a normal DRE result and a normal PSA level as screening criteria for prostate cancer is inadequate in the hypogonadal population. If those criteria alone had been followed, prostate cancer would have been missed in 11 of 77 men.

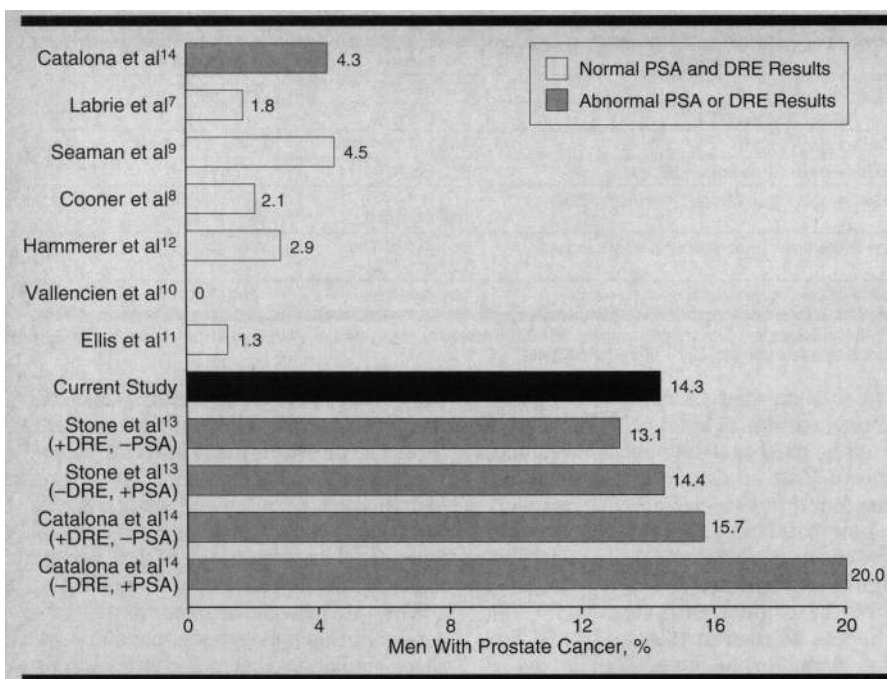
The cancer prevalence of 14% is severalfold higher than any reported previously for screening studies of men with normal PSA level and DRE finding. Several large prostate cancer screening studies have shown a prostate cancer prevalence of 1.8% to 4.5% when a negative DRE result was found in conjunction with a PSA level of 4.0 ng/mL or less.⁷⁻⁹ In those studies, biopsy was prompted by the presence of a suspicious area on transrectal ultrasound, suggesting that the true

prevalence of biopsy-detectable cancer in men with normal DRE results and PSA level may be even lower. This is supported by smaller studies that included routine examination of all men with prostate needle biopsy, for which the cancer prevalence for men with normal DRE results and PSA levels was 0% to 2.9%.¹⁰⁻¹²

The 14% prevalence of occult prostate cancer in this hypogonadal population is more similar to that noted among men with abnormal DRE findings or PSA levels than that among men without any clinical suspicion of cancer (Figure).⁷⁻¹⁴ These results suggest that men with low testosterone or free testosterone levels cannot be considered to have the same low risk of prostate cancer demonstrated historically for eugonadal men with normal PSA levels and DRE results. Moreover, the results of this clinical study, in which less than 1% of the prostate is sampled by systematic needle biopsies,¹⁵ cannot be compared with autopsy reports that describe a high incidence of microscopic prostate cancer, since the latter are based on serial step-sectioning of the entire gland.¹⁶

Although PSA level has proved to be a useful marker for prostate cancer in the general population,¹⁷ the clinical behavior of PSA level appears to be altered by naturally occurring reductions in testosterone or free testosterone levels.^{18,19} Whereas cancer normally produces a greater elevation of PSA level on a gram-for-gram basis than does benign tissue, accounting for higher PSA and PSAD values among men with cancer,^{17,20} PSA level and PSAD failed to distinguish men with cancer from those without cancer in this study. This suggests that cancer-induced elevations of PSA level may be a testosterone-mediated event, a hypothesis that heretofore has not been entertained.

It seems unlikely that the relatively high rate of occult prostate cancer in this study is caused by methodological variation or technical considerations. The mean and median ages in this study were less than 60 years, lower than all the cancer studies we referenced. Since the study population represented a consecutive series of men who underwent prostate bi-



Incidence of prostate cancer detected by transrectal ultrasound-guided biopsy in selected studies.

opsy in anticipation of testosterone therapy, there is no reason to suspect selection bias. Finally, although a cancer of a given size is more likely to be detected in a small prostate than in a larger one¹⁵ this explanation is unlikely to be operative in this case, since the mean prostate size of 35 mL corresponds to a moderately large gland, and prostate volumes were nearly identical in the cancer and benign groups. The most compelling ex-

planation of the data is that the normalizing effect of low androgen levels on DRE results and PSA levels masked the presence of a subgroup of men who would otherwise have been considered at high risk.

Although testosterone levels have been reported to have no influence on PSA levels for men with sexual dysfunction²¹ or prostate cancer,²² the group with abnormally low levels of testoste-

rone or free testosterone was not specifically examined. However, medical or surgical androgen ablation causes prompt reduction in PSA levels,²³ and finasteride has been shown to reduce PSA level by approximately 50% by means of blockade of dihydrotestosterone formation from testosterone.²⁴ Furthermore, clinical studies of hypogonadal men have shown elevation of PSA level associated with testosterone supplementation.^{18,19} This study suggests that naturally occurring reductions in testosterone or free testosterone level render PSA insensitive as a screening test for prostate cancer. It may thus prove useful to obtain testosterone and free testosterone levels together with PSA level to allow proper interpretation of prostate cancer risk and/or staging for a given individual.

These results support our initial hypothesis and clinical concern that the androgen sensitivity of prostate cancer may cause men with low testosterone or free testosterone levels to have falsely normal PSA levels and DRE results, thus masking the signs of cancer for some individuals. Since testosterone administration in hypogonadal men is associated with the potential risk of stimulating occult prostate cancer, it may therefore be prudent to perform prostate biopsy before testosterone replacement therapy is initiated, especially for men aged 60 years or older.

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