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PREVALENCE OF PROSTATE CANCER AMONG HYPOGONADAL MEN WITH PROSTATE-SPECIFIC ANTIGEN LEVELS OF 4.0 ng/mL OR LESS

ABRAHAM MORGENTALER AND ERNANI LUIS RHODEN

ABSTRACT

Objectives. To determine the prevalence of prostate cancer in hypogonadal men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less.

Methods. A total of 345 consecutive hypogonadal men with a PSA level of 4.0 ng/mL or less underwent evaluation with digital rectal examination and prostate biopsy before initiating a program of testosterone replacement therapy. All men had low serum levels of total or free testosterone, defined as less than 300 and 1.5 ng/dL, respectively.

Results. Cancer was identified in 15.1%. The cancer detection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/mL, respectively ($P < 0.05$). Cancer was detected in 26 (30.2%) of 86 men with a PSA level of 2.0 to 4.0 ng/mL. Cancer was detected in 21% of men with a testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL ($P = 0.04$). Men with free testosterone levels of 1.0 ng/dL or less had a cancer rate of 20% compared with 12% for men with greater values ($P = 0.04$). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile was 2.15 (95% confidence interval 1.01 to 4.55) for total testosterone and 2.26 (95% confidence interval 1.07 to 4.78) for free testosterone.

Conclusions. Prostate cancer was present in more than 1 of 7 hypogonadal men with PSA of 4.0 ng/mL or less. An increased risk of prostate cancer was associated with more severe reductions in testosterone. UROLOGY **68:** 1263–1267, 2006. © 2006 Elsevier Inc.

In the early 1990s, we began routinely performing prostate biopsy before the initiation of testosterone replacement therapy. In 1996, we reported that 11 (14%) of 77 hypogonadal men with a normal prostate-specific antigen (PSA) level and digital rectal examination (DRE) findings had cancer identified by sextant prostate biopsies.[1] Subsequent investigations have revealed that prostate cancer identified only because of low testosterone levels does not differ pathologically from cancer identified by standard indications (elevated PSA or abnormal DRE findings)[2] and that high-grade tumors are associated with low serum testosterone levels.[3,4]

We report our experience in a larger group of hypogonadal men with a PSA level of 4.0 ng/mL or less and investigated the possibility that more severe degrees of hypogonadism might be associated with an increased risk of prostate cancer.

MATERIAL AND METHODS

From June 1998 to December 2001, 345 consecutive men diagnosed with hypogonadism after referral for sexual dysfunction underwent prostatic evaluation before initiating a program of testosterone replacement therapy. All patients had low levels of total testosterone (TT) or free testosterone (FT), or both, and a PSA level of 4.0 ng/mL or less. Men taking medications known to lower PSA (finasteride or dutasteride) were excluded from this analysis.

The serum determinations of TT and FT were obtained during clinical hours ranging from 8 AM to 5 PM. The TT and FT levels were measured by radioimmunoassay (Diagnostic Products, Los Angeles, Calif). The FT assay used in this study has an r value of greater than 0.9 compared with equilibrium di-

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From the Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and Department of Urology, Federal Foundation of Medical Sciences of Porto Alegre, Porto Alegre, Brasil

Reprint requests: Abraham Morgentaler, M.D., One Brookline Place, Suite 624, Brookline, MA 02445. E-mail: amorgent@bidmc.harvard.edu

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TABLE I. *Characteristics of study population*

Patients (n)	345
Age (yr)	
Mean ± SD	58.9 ± 8.1
Range	40–84
PSA (ng/mL)	
Mean ± SD	1.44 ± 1.0
Median	1.1
TT (ng/dL)	
Mean ± SD	315.9 ± 130.3
Median	291
FT (ng/mL)	
Mean ± SD	1.07 ± 0.3
Median	1.1
Mean prostate volume (g)	34.6 ± 14.5
DRE findings (n)	
Normal	242 (70.1)
Abnormal	103 (29.9)
Mean No. of biopsies	6.75 ± 1.3

KEY: PSA = prostate-specific antigen; TT = total testosterone; FT = free testosterone; DRE = digital rectal examination.
Data in parentheses are percentages.

alysis.[5] TT levels less than 300 ng/dL and FT levels less than 1.5 ng/dL were considered subnormal for the purposes of this study. Clinical thresholds of 250 ng/dL or less for TT and 1.0 ng/dL or less for FT were used to categorize men as having more severe degrees of hypogonadism. A TT level of 250 ng/dL corresponded to the value noted in the Massachusetts Male Aging Study to be 2 standard deviations less than the mean for healthy men in their 40s.[6]

The PSA level was determined by radioimmunoassay using the Abbot IMX kit (Abbot Laboratories, Abbot Park, Ill). DRE was performed in all patients by a single urologist.

All men underwent transrectal ultrasonography of the prostate together with transrectal ultrasound-guided prostate needle biopsy. Six cores were routinely obtained, increasing to 10 to 12 systematically obtained cores if palpable or ultrasound abnormalities were observed.

Statistical analysis was performed using the Student *t* test, Mann-Whitney *U* test, and chi-square analysis to assess the differences between groups. Odds ratios with 95% confidence intervals were used for determination of prostate cancer risk by testosterone tertiles.

RESULTS

The characteristics of the study group are shown in Table I. The study included 345 men with a mean age of 58.9 years. Of these, 184 men (53.3%) had a TT level less than 300 ng/dL, and 327 (94.8%) had a FT level of less than 1.5 ng/dL. Of the 345 men, 23 were younger than 50 years, 12 had a TT level of 250 ng/dL or less, and 11 had TT level greater than 250 ng/dL. The PSA level was 4.0 ng/mL or less for all men, and the DRE findings were normal in 70.1%.

The biopsy results revealed 52 patients (15.1%) with prostate cancer and 293 (84.9%) without malignancy. Men with prostate cancer were slightly older than the men without cancer. No significant differences in TT, FT, and prostate volume were noted between men with cancer and those without cancer (Table II).

Men with abnormal DRE findings had a greater prevalence of cancer compared with men with normal DRE findings (Table II). The cancer rate was 25.6% in men whose biopsies involved more than six cores and was 9% in those with six cores only ($P = 0.0001$). This difference should be interpreted keeping in mind that the decision to perform more than six cores was made when a heightened concern of cancer was present, usually because of abnormal DRE findings, although the values may also simply reflect a greater yield from a larger number of biopsy cores. The DRE findings had a sensitivity of 38.5% and specificity of 71.6%.

Initial biopsy revealed 53 men with prostatic intraepithelial neoplasia without cancer. Of these 53 men, 41 underwent repeat prostate biopsy. Of the 41 men, 4 had cancer and were included in the cancer group and 37 had no evidence of malignancy and were included in the benign group. Finally, 12 refused repeat biopsy or were lost to follow-up and were included in the benign group.

The prevalence of prostate cancer by decade of age was 13% (3 of 23), 13.4% (24 of 178), 13.3% (14 of 105), and 28.2% (11 of 39) in men aged 40 to 49, 50 to 59, 60 to 69, and 70 years old or older, respectively. The cancer rate in men 70 years old or older was greater than the rest of the study group ($P < 0.05$).

Although all men in this study had a PSA level of 4.0 ng/mL or less, men with cancer still had a greater PSA level than those without cancer (2.07 ± 1.0 ng/mL versus 1.32 ± 0.9 ng/mL, respectively; $P = 0.001$). A linear relationship was noted between cancer risk and rising PSA level (Figure 1), with a cancer detection rate of 36.4% for men with a PSA level of 3.1 to 4.0 ng/mL. Overall, 26 of 86 men with a PSA level greater than 2.0 ng/mL had cancer (30.2%). The cancer rate was 10.0% among men with a PSA level of 2.0 ng/mL or less. No level of PSA was without risk, because men with a PSA level of 1.0 ng/mL or less still had a cancer rate of 5.6%.

The Gleason scores were distributed as follows: 1 case with Gleason score 5, 41 with Gleason score 6, 8 with Gleason score 7, and 3 with Gleason score 8. For men with a TT level of 250 ng/dL or less, 6 (26%) of 23 cancers had a Gleason score of 7 or greater compared with 6 (21%) of 29 for men with a TT level greater than 250 ng/dL. For FT, 7 (24.2%) of 29 men with FT of 1.0 ng/dL or less had cancer compared with 4 (17.4%) of 23 with FT greater than 1.0 ng/dL. These differences were not statistically significant. The mean age was older for men with a Gleason score of 7 or more (67.8 years versus 59.7 years, $P = 0.004$).

Prostate cancer risk correlated with testosterone levels (Fig. 2). Men with TT levels of 250 ng/dL or

TABLE II. *Clinical and laboratory features of men with and without prostate cancer*

Characteristic	Benign Biopsy	Prostate Cancer	*P* Value
Patients (n)	293 (84.9)	52 (15.1)	
Age (yr)			
Mean ± SD	58.4 ± 7.7	61.4 ± 9.8	0.01
Range	41–77	40–84	
PSA (ng/mL)	1.32 ± 1.0	2.07 ± 0.9	0.0001
TT (ng/dL)	318.2 ± 130.8	299 ± 127.5	0.35
FT (ng/dL)	1.08 ± 0.3	1.01 ± 0.3	0.12
Prostate volume (cm^3)	34.0 ± 15.8	38.3 ± 17.5	0.07
DRE (n)			
Normal	210 (86.8)	32 (13.2)	
Abnormal	83 (80.6)	20 (19.4)	0.02
Biopsies (n)	6.6 ± 1.1	7.6 ± 1.6	0.0001
Prostatic intraepithelial neoplasia (n)	53 (18.1)	25 (48.1)	0.0001

Abbreviations as in Table I.
Data presented as mean ± SD or numbers, with percentages in parentheses.

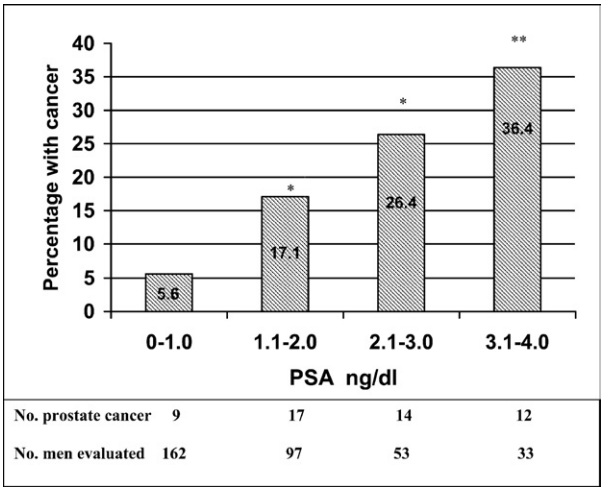

FIGURE 1. *Prostate cancer rates and PSA values for hypogonadal men. *P <0.05 versus men with PSA of 0 to 1.0 ng/mL. **P <0.05 versus men with PSA of 0 to 1.0 and 1.1 to 2.0 ng/mL.*

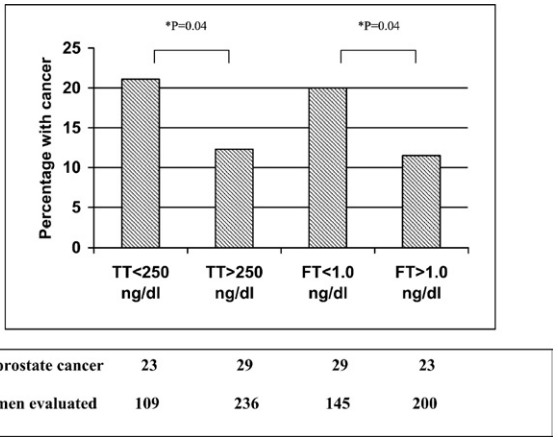

FIGURE 2. *Serum testosterone levels and prostate cancer rates.*

less had a greater rate of prostate cancer than men with levels greater than 250 ng/dL (21.1% versus 12.3%, respectively; $P = 0.04$). These two groups did not differ with regard to age, PSA level, DRE findings, or Gleason score. The odds ratio was 1.91 (95% confidence interval [CI] 1.05 to 3.49); with age adjustment, it was 2.02 (95% CI 1.10 to 3.72).

In addition, men with an FT level of 1.0 ng/dL or less had a greater rate of prostate cancer than men with an FT level greater than 1.0 ng/dL (20.0% versus 11.5%, respectively; $P = 0.04$). Men with an FT level of 1.0 ng/dL or less were slightly older than those with FT levels greater than 1.0 ng/dL by 1.8 years (60.1 years versus 58.3 years, respectively; $P = 0.02$) but did not differ with regard to PSA level, DRE findings, or Gleason score ($P > 0.05$). The odds ratio for FT decreased slightly with age adjustment, from 1.92 (95% CI 1.06 to 3.49) to 1.78 (95% CI 0.97 to 3.25). No significant Pearson correlation was noted between PSA and TT ($r = 0.05$, $P = 0.3$) or PSA and FT ($r = 0.07$, $P = 0.2$). There were 107 men who had both TT less than 250 ng/dL and FT less than 1.0 ng/dL. The cancer rate in these men was 19.6%.

The cancer rate was 20.9% for men with an FT level less than the median of 1.1 ng/dL and was 9.3% for men with an FT level greater than the median ($P = 0.03$). Although the cancer risk did not differ significantly for men with TT levels greater and less than the median of 291 ng/dL, a comparison of the lowest and highest tertiles for TT revealed a significantly increased risk of cancer for men with lower values (odds ratio 2.15, 95% CI 1.01 to 4.55). FT demonstrated a similarly increased risk of cancer for the lowest tertile compared with the highest (odds ratio 2.26, 95% CI 1.07 to 4.78). A comparison of the lowest FT tertile versus the combined middle and upper tertiles also demonstrated a significantly increased odds ratio of 1.90 (95% CI 1.05 to 3.46); however, this same

comparison for TT was not associated with an increased risk (odds ratio 1.73, 95% CI 0.95 to 3.16).

COMMENT

The results of this retrospective study confirm and extend our previous findings that a sizable proportion of hypogonadal men has biopsy-detectable prostate cancer despite normal PSA levels.[1] In addition, the combination of low serum testosterone and PSA level greater than 2.0 ng/mL appears to be particularly worrisome for the presence of cancer, because 30.2% of such men in this study had positive biopsy findings. Moreover, this study for the first time presents data showing that lower testosterone levels are associated with an increased risk of cancer.

In 1996, we presented biopsy results in 77 hypogonadal men with normal DRE findings and PSA level of 4.0 ng/mL or less, finding 11 cancers for a cancer rate of 14%.[1] This larger series has confirmed those results, with a cancer rate of 15.1% overall, including 13.2% in men with normal DRE findings. Thus, approximately 1 in 7 hypogonadal men with a PSA level of 4 ng/mL or less has biopsy-detectable cancer. This cancer prevalence is almost identical to the 15.2% cancer rate among men with PSA levels of 4.0 ng/mL or less noted by Thompson *et al.*[7] in the placebo arm of the Prostate Cancer Prevention Trial. These results suggest that hypogonadism offers little protection against the development of biopsy-detectable prostate cancer.

Perhaps the most important finding in this study was that lower levels of TT or FT were associated with an increased risk of cancer. The risk of cancer was doubled for men with TT less than 250 ng/dL and for men in the lowest tertile for either TT or FT compared with men in the highest tertile. To the best of our knowledge, this appears to be the first report linking lower serum testosterone with increased prostate cancer risk.

These somewhat surprising results fit into a growing body of data suggesting a relationship between low serum testosterone and prostate cancer. For instance, low serum testosterone has been associated with high-grade prostate cancer,[3,4] more aggressive disease,[8] advanced pathologic stage at radical prostatectomy,[9,10] and shorter survival.[11] Men with prostate cancer have lower circulating androgen bioreactivity,[12] and low testosterone in men with prostate cancer is associated with greater microvessel density.[13] Finally, it is the natural history of prostate cancer to become highly prevalent when men are older and testosterone levels have declined.

It remains to be determined whether the association of low testosterone with prostate cancer is causal, and if so, whether low testosterone contributes to development of prostate cancer, or whether prostate cancer causes low testosterone. The latter possibility is supported by the observation that levels of serum testosterone increase after radical prostatectomy, suggesting that prostate cancer itself may secrete an agent that suppresses testosterone.[14,15] It has been postulated elsewhere that low serum testosterone may be a marker for prostate cancer.[16] Our earlier results, and the results of this study, support this possibility.

Although prostate cancer prevalence normally correlates strongly with age, in these hypogonadal men the cancer risk remained almost identical for men in the fifth, sixth, and seventh decades. This level degree of risk for three decades raises the possibility that these men shared a common risk factor, namely low testosterone, that trumped age or other risk factors.

This study had several limitations, including the lack of a control group, variability in testosterone assays and results, the possibility of overdetection and underdetection of prostate cancer, lack of standardization regarding the number of biopsy cores, and the nature of the study population. Nevertheless, this study presents a first attempt to investigate the relationship of the severity of testosterone reduction to the prevalence of biopsy-detectable prostate cancer, and the results appear to warrant more rigorous further investigation.

CONCLUSIONS

This study has revealed that a substantial number of hypogonadal men have biopsy-detectable prostate cancer, even with normal DRE findings and PSA level of 4.0 ng/mL or less. The risk of cancer was doubled for men with the lowest testosterone values and was particularly worrisome when low testosterone levels were combined with PSA levels of 2.0 ng/mL or greater. The relationship between low serum testosterone and prostate cancer risk merits further investigation.

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