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THE PROSTATIC SPECIFIC ANTIGEN ERA IS ALIVE AND WELL: PROSTATIC SPECIFIC ANTIGEN AND BIOCHEMICAL PROGRESSION FOLLOWING RADICAL PROSTATECTOMY

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ABSTRACT

Purpose: Prostate specific antigen (PSA) has been shown to predict the presence of prostate cancer on biopsy, pathological stage, and biochemical progression following primary therapy. A recent study found only a weak association between PSA and tumor volume in the radical prostatectomy (RP) specimen and concluded that the PSA era is over. We examined the association between PSA and clinical progression in men undergoing RP.

Materials and Methods: The study population consisted of 2,312 men treated with RP between 1992 and 2004 by a single surgeon. We evaluated the association between preoperative PSA and biochemical progression on multivariate analysis.

Results: Men with higher preoperative PSA concentrations had higher grade cancers in the biopsy and RP specimen, and more adverse pathological features. After adjusting for the clinical covariates of age, race, grade, stage, and year of surgery, preoperative PSA was significantly associated with the risk of biochemical progression. When only men with PSA less than 10 ng/ml were examined, PSA remained a significant predictor of biochemical progression on multivariate analysis (RR 1.30, 95% CI 1.18 to 1.44, $p < 0.001$). For each 2-point increase in PSA, the risk of biochemical progression increased approximately 2-fold.

Conclusions: Preoperative PSA was significantly associated with high grade disease and adverse pathological findings. After adjusting for clinical covariates, PSA was significantly associated with the risk of biochemical progression, even in men with PSA less than 10 ng/ml. Despite multiple limitations, PSA remains the best prostate cancer tumor marker available.

KEY WORDS: prostate, prostate-specific antigen, prostatic neoplasms, prostatectomy

The Food and Drug Administration approved prostate specific antigen (PSA) testing to monitor men with prostate cancer in 1986. It rapidly became apparent that PSA was also a valuable tool for detecting early stage prostate cancer,[1,2] and staging men with newly diagnosed disease.[3] Introduction of PSA screening resulted in a large cull effect of detecting prevalent disease, as evident by a dramatic increase in the incidence of new cases and a dramatic decrease in the incidence of advanced disease.[4] However, in the modern PSA era, the value of PSA to detect incident disease has been questioned due to evidence from 2 sources. The first is increasing awareness that men with normal PSA can have prostate cancer. This was exemplified by the Prostate Cancer Prevention Trial (PCPT), where on the end of study biopsy almost 15% of men with PSA less than 4 ng/ml had prostate cancer on sextant biopsy.[5] Therefore, what cutoff defines increased PSA has become unclear. The second line of evidence to question the value of PSA comes from a recent study, which found that PSA was only weakly associated with prostate cancer volumes in men treated with radical prostatectomy (RP).[6] This observation lead the authors of this study to proclaim, "The prostate specific antigen era in the United States is over for prostate cancer."[6] However, tumor volume may not be the optimal end point. While larger tumors usually correlate with worse outcomes, this is not always true.[7] The more clinically relevant question is, "What is the relationship between PSA and progression?" Specifically, in men with PSA less than 10 ng/ml, some[8,9] but not all studies[10–12] found that lower PSA values were associated with better outcomes. To examine whether preoperative PSA correlates with outcome following RP, especially in men with PSA less than 10 ng/ml, we examined the association between preoperative PSA and biochemical progression in men treated by a single surgeon spanning the entire PSA era.

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MATERIALS AND METHODS

Study population and clinicopathological variables. After obtaining Institutional Review Board approval and informed consent when necessary, 2,371 consecutive patients treated with anatomical RP for prostate adenocarcinoma by 1 surgeon (PCW) from 1992 to 2004 at The Johns Hopkins Hospital were identified. Two men with missing PSA data were excluded. Men treated with preoperative hormonal (luteinizing hormone-releasing hormone agonist, antiandrogen or 5α-reductase type II inhibitor) therapy (30), chemotherapy (2), or radiation therapy (2) were excluded. Men diagnosed from a transurethral resection (TUR) specimen (clinical stage T1a/T1b) were excluded (23) because this could affect PSA measurements. This resulted in a study population of 2,312 men. Only 4 men received adjuvant radiation and no patient received hormonal therapy prior to biochemical progression (a single PSA 0.2 ng/ml or greater). These 4 men were censored

at the time of adjuvant therapy. Prostatectomy specimens were sectioned as previously described.[13]

Statistical analysis. We explored differences in the distribution of clinicopathological characteristics among PSA groups of less than 10, 10 to 19.9 and 20 or greater ng/ml using ANOVA for continuous variables and the chi-square test for categorical variables. Age at RP and year of surgery were considered continuous variables, while race (black and other vs white), clinical stage (T2a, T2b and T2c/T3a vs T1c), and Gleason sum (3 + 4 and 4 + 3 or greater vs 2 to 6) were considered categorical variables.

Time to biochemical progression was compared among the groups using Kaplan-Meier plots and the log rank test. To estimate the RR of progression associated with PSA, we used a Cox proportional hazards regression model. PSA was entered into the model as a series of indicator variables for each PSA category. We tested for trend by entering the median PSA of each PSA category as a continuous term into the model and evaluating the coefficient by the Wald test. We ran several Cox regression models, first with PSA alone (crude), then with PSA and age (age adjusted), and finally with PSA and the clinical covariates age, race, biopsy Gleason sum, clinical stage and year of surgery. Point estimates for the crude and age adjusted models were similar and, therefore, results are only shown for the age adjusted and fully adjusted models.

For analyses in men with PSA less than 10 ng/ml, PSA was grouped as a categorical variable of less than 2, 2 to 3.9, 4 to 5.9, 6 to 7.9, and 8 to 9.9 ng/ml. The distribution of clinicopathological characteristics among PSA groups was examined using ANOVA for continuous variables or the chi-square test for categorical variables. The RR of progression associated with PSA was estimated using a Cox proportional hazards regression model, as described. All statistical analyses were performed using STATA 8.0 (StataCorp., College Station, Texas).

RESULTS

Patient demographics. Men with higher PSA were significantly more likely to have higher clinical stages, higher grade cancers in the biopsy and final RP specimen, positive surgical margins, capsular penetration, seminal vesicle invasion, and lymph node metastasis (each $p < 0.001$, table 1). Preoperative PSA was also significantly related to age at surgery with men in whom PSA was between 10 and 19.9 ng/ml being the oldest patients ($p < 0.001$).

PSA and biochemical progression. During a mean followup ± SD of 4.8 ± 3.1 years (median 4), 211 men (10%) had biochemical progression. Increasing PSA was significantly associated with increased risk of biochemical progression (log rank $p < 0.001$, fig. 1). The 5-year PSA free survival rates in men with PSA less than 10, 10 to 19.9, and 20 or greater ng/ml were 94% (95% CI 93 to 95), 77% (95% CI 71 to 81) and 53% (40 to 65), respectively. After adjustment for the clinical characteristics of age at RP, year of RP, race, clinical stage, and biopsy Gleason sum, preoperative PSA was significantly associated with increased risk of biochemical progression ($p < 0.001$, table 2). Relative to men with PSA less than 10 ng/ml, men with PSA between 10 and 19.9 ng/ml were more than 3 times more likely to progress (RR 3.1, 95% CI 2.3 to 4.2) and men with PSA 20 ng/ml or greater were more than 5 times more likely to progress (RR 5.2, 95% CI 3.3 to 8.0). In addition, PSA as a continuous variable was significantly related to biochemical progression (RR 1.07, 95% CI 1.06 to 1.08, $p < 0.001$, table 2)

Analysis of men with PSA less than 10 ng/ml. Given that the finding of a positive association between increased PSA and biochemical progression was likely in large part due to poor outcomes in men with high PSA, we explored whether PSA remained significantly predictive of outcome in men with a more narrowly defined PSA range. Therefore, we examined the association between PSA, and clinicopathological characteristics and biochemical progression in 1,902 men with preoperative PSA value less than 10 ng/ml. In men with preoperative PSA less than 10 ng/ml, higher PSA was significantly associated with older age ($p < 0.001$), higher clinical stages ($p < 0.001$), higher grade cancers in the biopsy ($p < 0.001$) and final RP specimen ($p < 0.001$), positive surgical margins ($p = 0.001$), capsular penetration ($p < 0.001$), and seminal vesicle invasion ($p = 0.003$, table 3). There was no significant association between PSA and lymph node metastasis ($p = 0.13$), although the incidence of lymph node metastasis was low in all groups.

In men with PSA less than 10 ng/ml, increasing PSA was significantly associated with increased risk of biochemical progression (log rank $p < 0.001$, fig. 2). After adjustment for the clinical characteristics of age at RP, year of RP, race, clinical stage, and biopsy Gleason sum, preoperative PSA was significantly associated with increased risk of biochemical progression ($p < 0.001$, table 4). For each 2-point increase in PSA, the risk of biochemical progression approximately doubled (table 4). In addition, when PSA was examined as a continuous variable, it remained significantly associated with biochemical progression (RR 1.30, 95% CI 1.18 to 1.44, $p < 0.001$, table 4).

TABLE 1. *Clinical and pathological features in men undergoing RP segregated by preoperative PSA*

	Preop PSA (ng/ml)			p Value
	Less Than 10	10–19.9	20 or Greater	
No. pts	1,902	346	64	
Mean age at surgery ± SD	56.2 ± 6.8	58.0 ± 6.3	56.7 ± 6.9	<0.001 (ANOVA)
No. biopsy Gleason sum (%):				<0.001 (chi-square test)
2–6	1,584 (83)	256 (74)	36 (56)	
7 (3 + 4)	231 (12)	56 (16)	16 (25)	
4 + 3 or Greater	87 (5)	34 (10)	12 (19)	
No. clinical stage (%):				<0.001 (chi-square test)
T1c	1,271 (67)	225 (65)	39 (61)	
T2a	446 (23)	66 (19)	8 (13)	
T2b	140 (7)	39 (11)	9 (14)	
T2c	33 (2)	12 (3)	6 (9)	
T3	12 (1)	4 (1)	2 (3)	
No. pathological Gleason score (%):				<0.001 (chi-square test)
2–6	1,382 (73)	179 (52)	12 (19)	
7 (3 + 4)	378 (20)	99 (29)	26 (41)	
4 + 3 or Greater	142 (7)	68 (20)	26 (41)	
No. pos surgical margins (%)	129 (7)	47 (14)	19 (30)	<0.001 (chi-square test)
No. capsular penetration (%)	511 (27)	164 (47)	48 (75)	<0.001 (chi-square test)
No. seminal vesicle invasion (%)	55 (3)	39 (11)	15 (23)	<0.001 (chi-square test)
No. pos lymph nodes (%)	28 (1)	31 (9)	21 (33)	<0.001 (chi-square test)