Prostate Cancer Detection in Men With Serum PSA Concentrations of 2.6 to 4.0 ng/mL and Benign Prostate Examination

Enhancement of Specificity With Free PSA Measurements

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Objective.—To determine the detection rate of prostate cancer in a screening population of men with prostate-specific antigen (PSA) concentrations of 2.6 to 4.0 ng/mL and a benign prostate examination, to assess the clinicopathological features of the cancers detected, and to assess the usefulness of measuring the ratio of free to total PSA to reduce the number of prostatic biopsies.

Design.—A community-based study of serial screening for prostate cancer with serum PSA measurements and prostate examinations.

Setting.—University medical center.

Subjects.—A total of 914 consecutive screening volunteers aged 50 years or older with serum PSA levels of 2.6 to 4.0 ng/mL who had a benign prostate examination and no prior screening tests suspicious for prostate cancer, 332 (36%) of whom underwent biopsy of the prostate.

Main Outcome Measures.—Cancer detection rate, clinical and pathological features of cancers detected, and specificity for cancer detection using measurements of percentage of free PSA.

Results.—Cancer was detected in 22% (73/332) of men who underwent biopsy. All cancers detected were clinically localized, and 81% (42/52) that were surgically staged were pathologically organ confined. Ten percent of the cancers were clinically low-volume and low-grade tumors, and 17% of those surgically staged were low-volume and low-grade or moderately low-grade tumors (possibly harmless). Using a percentage of free PSA cutoff of 27% or less as a criterion for performing prostatic biopsy would have detected 90% of cancers, avoided 18% of benign biopsies, and yielded a positive predictive value of 24% in men who underwent biopsy.

Conclusions.—There is an appreciable rate of detectable prostate cancer in men with serum PSA levels of 2.6 to 4.0 ng/mL. The great majority of cancers detected have the features of medically important tumors. Free serum PSA measurements may reduce the number of additional biopsies required by the lower PSA cutoff.

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MEASUREMENT of serum prostate-specific antigen (PSA) concentration is widely used to aid in the early detection of prostate cancer.[1] Although a PSA cutoff of 4.0 ng/mL is most often used for screening, more than 20% of men with diagnosed prostate cancer have PSA levels lower than this value.

Except for men aged 40 to 59 years old, physicians usually do not recommend biopsies in men whose PSA levels are lower than 4.0 ng/mL unless the digital prostate examination is abnormal. However, prostate cancer can be detected within 3 to 5 years in 13% to 20% of men whose total PSA levels are between 2.6 and 4.0 ng/mL.[2-4] Since about 30% of men with PSA levels between 4.0 and 10.0 ng/mL have cancers that have extended beyond the prostatic capsule at the time of diagnosis,[5-7] detecting these cancers earlier should enable more men to seek treatment while their cancer is still curable. However, in striving for earlier detection, it is important to limit the number of unnecessary additional biopsies performed.

One strategy for reducing unnecessary biopsies is to measure the ratio of free to total PSA.[8-11] Studies have demonstrated clinical usefulness of free PSA measurements in men with total serum PSA concentrations of 4.0 to 10.0 ng/mL.[2,8,10-13]

We evaluated the prevalence and clinicopathological features of prostate cancer in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and a palpably benign prostate examination, and whether measuring the percentage of free PSA could reduce the additional biopsies required by the lower PSA cutoff.

METHODS

Subjects and Procedures

We report on the results of the Washington University PSA-3 prostate cancer screening study conducted from May 1995 through October 1996, when 14 193 men aged 50 years or older (range, 50-90 years; mean [±SD] age, 62 [±7] years) were screened with serum PSA measurement and digital prostate examination. These men responded to a press release asking healthy men to participate in a study of PSA measurement as a screening test for prostate cancer. Only 6% of the screening volunteers were nonwhite.

Eighty-five percent of the men had been enrolled in our PSA-2 longitudinal screening study,[7,14,15] which extended from May 1991 through April 1995, and had been previously screened with both PSA measurement and prostate examination (mean number of prior screening visits [±SD], 3.8 [±1.7], and mean number of years [±SD] since study entry, 2.6 [±1.1]).

In the PSA-3 study protocol, we screened all men with PSA testing and digital prostate examination at 6-month intervals. If the PSA measurement was higher than 2.5 ng/mL or the prostate examination was suspicious for cancer, we recommended systematic ultrasound-guided sextant needle biopsies of the prostate. The PSA-3 study protocol was approved by the Washington University Human Studies Committee, and informed consent was obtained from all volunteers.

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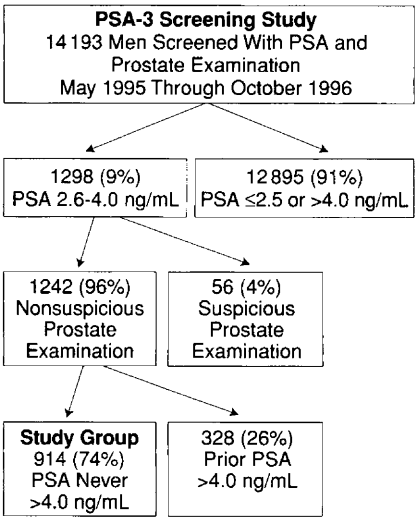

Figure 1.—Selection of final study group (n=914) from 14 193 men screened with prostate-specific antigen (PSA) and prostate examination from May 1995 through October 1996. Eighty-five percent of the men screened between May 1995 and October 1996 had been previously enrolled in the PSA-2 screening study (May 1991 through April 1995).

All PSA determinations were performed with an immunoenzymetric assay (Tandem-E PSA, Hybritech Inc, San Diego, Calif) (normal range, 0-4.0 ng/mL).[6] In men with a total serum PSA level of 2.6 ng/mL or higher, we measured serum free PSA using the Hybritech Tandem-R free PSA assay.[11] We calculated the percentage of free PSA as the ratio of free PSA to total PSA, multiplied by 100.

In addition to free and total PSA measurements, the following were recorded: (1) prostate examination findings, categorized as normal, abnormal but benign, or suspicious; (2) prostate volume based on transrectal ultrasound scan (calculated via the prolate spheroid formula)[16]; (3) biopsy results; (4) clinical[5] and pathological[6] tumor stage; (5) tumor grade; and (6) percentage of cancer in the surgical specimen.

Of the 14 193 men screened between May 1995 and October 1996, 1298 (9%) had a serum PSA concentration between 2.6 and 4.0 ng/mL, of whom 1242 (96%) had a nonsuspicious prostate examination. We excluded 328 additional men (26%) who had previously (ie, before May 1, 1995) had a serum PSA concentration higher than 4.0 ng/mL and/or a suspicious prostate examination, leaving a final study group of 914 men (Figure 1). The percentage of free PSA could not be calculated in 5% of the men because of insufficient serum (n=40) or error in performing the free PSA assay (n=10).

Statistical Analysis

We used t tests and χ^2 statistics to determine if clinical characteristics including race, age, number of screening visits, serum PSA concentration, and percentage of free PSA differed for men who underwent the recommended biopsy within 18 months compared with those who did not. For the men previously enrolled in the PSA-2 study (n=752 [82% of the sample]), we also compared PSA rate of change for the men who underwent biopsy vs those who waived biopsy. The PSA rate of change was calculated as the serum PSA measurement from the most recent screening visit minus the PSA measurement from the initial visit at PSA-2 study entry, divided by the number of years since PSA-2 study entry.

In the 332 men who underwent biopsy, we computed t tests and χ^2 statistics to compare the above clinical characteristics (with the addition of estimated prostate volume and PSA density [total PSA/estimated volume][17]) for those with and without prostate cancer. Clinical characteristics associated with presence of prostate cancer within univariate analyses ($P \leq .10$) also were included in an unconditional multivariate logistic regression model to predict presence of cancer. Before calculating the logistic model, we confirmed the assumption of a linear relationship with the presence of cancer for continuously scaled predictors.[18] Consequently, we modeled these predictors as simple linear effects. We report the Wald χ^2 value and adjusted odds ratio (OR) for each significant predictor. The adjusted OR represents increased risk for prostate cancer, controlling for other predictors.

In the subset of men with cancer, we report clinical stage, biopsy Gleason score, and in those men who underwent radical prostatectomy, pathological stage, prostatectomy specimen Gleason score, and percentage of cancer in the surgical specimen.

To assess whether the percentage of free PSA would increase the specificity of PSA-based screening, we preset sensitivity at 90% and determined the cutoff for the percentage of free PSA. We then computed specificity (ie, the proportion of unnecessary biopsies) using the identified percentage of free PSA cutoff.

Table 1.—Distribution of Clinical Characteristics for 914 Screening Volunteers With Prostate-Specific Antigen (PSA) Concentrations of 2.6 to 4.0 ng/mL and Benign Prostate Examination, Stratified by Whether They Underwent a Prostatic Biopsy

	Total Sample (N=914)	Underwent Biopsy (n=332)	Waived Biopsy (n=582)	P
Race, No. (%)				
Black	43 (4.7)	16 (37.2)	27 (62.8)	.90*
White, Hispanic, or Asian	871 (95.3)	316 (36.3)	555 (63.7)	
Current age, mean (±SD), y	64.6 (±7.9)	64.2 (±7.2)	64.8 (±8.3)	.20
No. of prior screening visits, mean (±SD)	2.9 (±2.0)	3.2 (±2.0)	2.9 (±2.1)	.03
Total PSA, mean (±SD), ng/mL	3.1 (±0.4)	3.2 (±0.4)	3.1 (±0.4)	.04
PSA rate of change per year, mean (±SD)†	0.3 (±0.6)	0.4 (±0.6)	0.3 (±0.5)	.40
Percentage of free PSA, mean (±SD)†	20.1 (±7.9)	19.9 (±7.8)	20.2 (±7.9)	.60

*P value for χ^2 test for comparison of the proportion of men who underwent biopsy, stratified by race. All other P values correspond to 2-tailed t tests for comparison of means for continuously scaled clinical characteristics in men with and without biopsy.

†PSA rate of change not available for 162 men without prior screening visits and percentage of free PSA measurements unavailable for 50 men.

RESULTS

Clinical Characteristics of Screening Volunteers

The clinical characteristics for study volunteers are shown in Table 1. The majority of the men were white, older than 60 years, and had been prescreened with PSA testing and prostate examination.

Comparison of Men Who Underwent Biopsy vs Men Who Waived Biopsy

Biopsy was performed within 18 months of the recommendation in 332 (36%) of 914 men. Compared with the men who waived biopsy, the men who underwent biopsy had a slightly higher total serum PSA level (mean [SD] total PSA, 3.2 [±0.4] vs 3.1 [±0.4]; P=.04) and more prior screening visits (mean total prior visits, 3.2 [±2.0] vs 2.9 [±2.1]; P=.03; see Table 1). Otherwise no significant differences were observed between men who underwent biopsy and those who did not (Table 1).

Prediction of Cancer Based on Clinical Characteristics

Prostate cancer was detected in 73 (22%) of the 332 men who underwent biopsy. Table 2 summarizes clinical characteristics stratified by presence or absence of cancer. Cancer was significantly associated with more prior screening visits (P=.03), lower prostate volume (P=.03), and higher PSA density (P=.01). Nonsignificant trends were also found for black race (P=.10) and lower percentage of free PSA (P=.10). In this population, cancer was not associated with age (P=.20), PSA rate of change (P=.60), or total serum PSA level (P=.70).

The multivariate logistic regression model for prediction of cancer based on

the number of prior screening visits, PSA density, race, and percentage of free PSA (prostate volume was not included due to its overlap with PSA density, $r=-0.7$; $P<.001$) indicated significant effects for number of prior visits (Wald $\chi^2=3.9$; $P=.05$; adjusted OR, 1.2 [95% confidence interval (CI), 1.0-1.3] per each increase in number of visits) and PSA density (Wald $\chi^2=5.7$; $P=.02$; adjusted OR, 1.3 [95% CI, 1.1-1.5] per each 0.03 increase in PSA density). A trend was also found for black race (Wald $\chi^2=2.2$, $P=.10$; adjusted OR, 2.5 [95% CI, 0.8-8.2] for black race).

Stage and Grade of Cancers Detected

All of the cancers detected were clinically localized and the median biopsy Gleason score was 6 (Table 3). Seven (10%) of 73 men had both low-volume and low-grade tumors (less than 5% cancer and Gleason score less than 5) on biopsy.

Of 73 men, 52 (71%) underwent radical prostatectomy, and 42 (81%) had pathologically organ-confined cancer (Table 3). The median surgical specimen Gleason score was 6 (Table 3). The distribution of percentage of cancer in the surgical specimen is shown in Table 3.

Of the men with surgically staged tumors for whom percentage of cancer was available, 7 (17%) of 42 were both low-volume (<1% cancer and no evidence of capsular penetration) and low-grade or moderately low-grade tumors (Gleason score <7).

Percentage of Free PSA as a Means to Reduce Biopsies With Lower Total PSA Screening Cutoffs

Figure 2 shows the distribution of percentage of free PSA as a function of the total PSA of men with and without prostate cancer. To determine whether the percentage of free PSA could reduce unnecessary biopsies, we calculated the percentage of free PSA cutoff point that would predict cancer with at least 90% sensitivity. This cutoff was 27% free PSA (95% CI, 12.9-23.0) and would have avoided 18% of negative biopsies.

Setting sensitivity to at least 90% would have resulted in 8 missed cancers. All were clinically localized and had biopsy Gleason scores less than 7. Of the 4 men who underwent radical prostatectomy, all had organ-confined disease, with Gleason scores less than 7, and 5% or less tumor volume.

COMMENT

No previous study has systematically evaluated the cancer detection rate in men with PSA levels in the range of 2.6 to 4.0 ng/mL and a normal prostate examination. Our results show that 22% of men who underwent biopsy had prostate cancer detected with 6-sector biopsies. Although we previously reported a lower cancer detection rate (7%) in men with PSA levels between 2.9 and 4.0 ng/mL, in that study, biopsies were only directed at palpable or sonographic abnormalities.[19] After 4 years of serial screening, the cumulative cancer detection rate was approximately 20% in that cohort.[4]

Because higher screening cutoffs are well established, only 36% of our subjects complied with the recommended biopsy; however, no obvious selection bias could be determined. However, the men who underwent biopsy had slightly higher PSA levels and had been screened more often. These differences are unlikely to have introduced a selection bias for biopsy.

Using the lower PSA cutoff, the great majority of cancers detected had favorable histopathological features, with approximately 80% being pathologically organ confined. This compares with about 70% organ-confined cancers with PSA levels higher than 4.0 ng/mL.[6,7] Since 17% were pathologically low-volume and low-grade or moderately low-grade tumors, the use of the lower PSA cutoff did not appear to substantially increase the detection of medically unimportant cancers. Using a similar definition for insignificant cancer, Epstein et al[20] found in a clinical series of men with stage T1c prostate cancer that approximately 17% would be classified as having insignificant cancer.

Table 2.—Distribution of Clinical Characteristics for 332 Screening Volunteers Who Underwent Biopsy, Stratified by Presence or Absence of Prostate Cancer

	Cancer Detected (n=73)	Cancer Not Detected (n=259)	P
Race, No. (%)			
Black	6 (37.5)	10 (62.5)	.10*
White, Hispanic, or Asian	67 (21.2)	249 (78.8)	
Current age, mean (±SD), y	65.2 (±7.5)	63.9 (±7.1)	.20
No. of prior screening visits, mean (±SD)	3.7 (±2.2)	3.1 (±1.9)	.03
Total PSA, mean (±SD), ng/mL	3.2 (±0.4)	3.2 (±0.4)	.70
PSA rate of change per year, mean (±SD)†	0.3 (±0.7)	0.4 (±0.5)	.60
Estimated prostate volume, mean (±SD), cm^3†	33.7 (±14.5)	39.6 (±20.1)	.03
PSA density, mean (±SD)†	0.11 (±0.05)	0.09 (±0.04)	.009
Percentage of free PSA, mean (±SD)†	18.8 (±6.9)	20.2 (±7.9)	.10

*P value for χ^2 test for comparison of the proportion of men with cancer detected, stratified by race. All other P values correspond to 2-tailed t tests for comparison of means for continuously scaled clinical characteristics in men with and without cancer detected.

†PSA rate of change not available for 47 men without prior screening visits, estimated prostate volume unavailable for 17 men, and percentage of free PSA measurements unavailable for 15 men.

Table 3.—Distribution of Stage and Grade for 73 Cancers Detected

	No. (%)
Clinical stage localized	73 (100)
Gleason score based on biopsy specimen	
≤4	9 (12.3)
5-6	58 (79.4)
≥7	6 (8.2)
Initial treatment	
Pending treatment	2 (2.7)
Observation	12 (16.4)
Hormonal therapy	3 (4.1)
Radiation therapy	4 (5.5)
Radical prostatectomy	52 (71.2)
Pathological stage	
Organ-confined*	42 (80.7)
Gleason score based on surgical specimen†	
≤4	2 (3.9)
5-6	43 (84.3)
≥7	6 (11.8)
Percentage of cancer in surgical specimen†	
≤1	7 (16.7)
2-5	21 (50.0)
6-10	11 (26.2)
>10	3 (7.1)

*Of the 10 men with non–organ-confined disease, 6 had unilateral positive margins or extracapsular extension (pT3a), Gleason scores ranging from 5 to 7, and 2% to 8% cancer in the surgical specimen; 2 had bilateral positive margins or extracapsular extension (pT3b), Gleason scores of 6 or 7, and 5% to 10% cancer in the specimen; and 1 had seminal vesicle invasion (pT3c), a Gleason score of 7, and 40% cancer in the specimen.

†Gleason score for surgical specimen was not available for 1 man, and percentage of cancer in surgical specimen not available for 10 men.

Using a free PSA cutoff of 27% as a criterion for biopsy would have detected 90% of the cancers and avoided 18% of unnecessary biopsies, yielding a positive predictive value of 24% in the men who underwent biopsy. Therefore, percentage of free PSA would provide modest biopsy savings against the potential 2-fold increase in additional biopsies that would be recommended with a lower total PSA cutoff.

While avoiding unnecessary biopsies is desirable, missing 10% of the cancers is of concern. However, a decrease in sensitivity may be more acceptable in this PSA range because in current practice, most men with a PSA level of 2.6 to 4.0 ng/mL and a normal prostate examination would not be subjected to biopsy.

Our results suggest that demographically comparable men with PSA levels of 2.6 to 4.0 ng/mL should consider having a percentage of free PSA measured and that a biopsy should be considered in those with less than 27% free PSA. Based on our results from the first screening visit only (and assuming 80% compliance with biopsy recommendation in men with PSA levels greater than 4.0 ng/mL and/or suspicious prostate examination,[15] and 36%

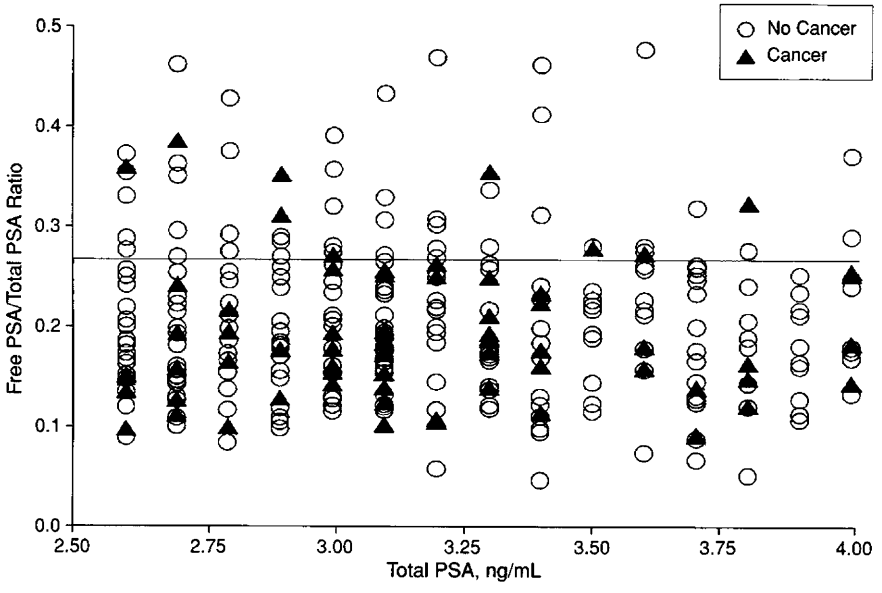

Figure 2.—Percentage of free prostate-specific antigen (PSA) and total PSA concentration in 72 men with prostate cancer and 245 men without prostate cancer. Cutoff point of 27% for greater than 90% sensitivity eliminates 18% (95% confidence interval, 12.9-23.0) of biopsies in men without cancer.

compliance in men with PSA levels of 2.6 to 4.0 ng/mL with a nonsuspicious prostate examination), using this strategy in our screening program would have increased the number of recommended biopsies by 40%, increased the number of actual biopsies performed by 18%, and increased cancer detection by 15%, while yielding a positive predictive value of 24% in men who are recommended to have sextant biopsies.

Lowering the recommended PSA level to 2.5 ng/mL for biopsy may be especially beneficial for black men whose incidence of prostate cancer is nearly 40% higher than in white men and whose cancers are more likely to be missed by standard age-specific PSA reference ranges determined from white populations.[21] Black men also are more likely to have advanced prostate cancer at the time of diagnosis and are more likely to die from the disease.[22] In our screening population of men with PSA levels in the range of 2.6 to 4.0 ng/mL, there was also a trend for black race to predict prostate cancer. Although our sample was small (only 16 black men underwent biopsy), a higher proportion of black men had cancer compared with nonblack men (38 vs 21%; see Table 2). We have reported similar racial differences in a larger sample of black and white men who had undergone biopsy based on a PSA level of more than 4.0 ng/mL and/or suspicious prostate examination.[15]

In conclusion, men with total PSA levels in the range of 2.6 to 4.0 ng/mL have an appreciable prevalence (22%) of detectable prostate cancer, and the majority of cancers detected appear to be medically important. Our results also suggest that the use of free PSA measurements may reduce unnecessary biopsies in selected men with serum PSA levels of 2.6 to 4.0 ng/mL and a normal prostate examination.

Detecting cancers in men with these PSA levels may help reduce the prostate cancer mortality and morbidity rates. However, we cannot exclude the alternative possibility that the outcomes would be similar if the biopsy had been delayed until the PSA level increased to 4.0 ng/mL. Further, we do not yet have definitive data that early cancer detection via screening with any PSA cutoff improves patient outcomes.

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