

Detection of Prostate Cancer at Low and Intermediate Serum Prostate-Specific Antigen Levels in a Country with a Low Incidence of Prostate Cancer

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Background: The objective of this study was to evaluate the cancer detection rate and the pathologic findings of biopsy in men at low and intermediate prostate-specific antigen (PSA) levels in an Asian population.

Methods: Patients between 40 and 79 years were entered into a study and 755 patients with serum PSA level of 2.0–10.0 ng/ml underwent trus-guided systematic biopsy. Patients were divided to low (PSA 2.0–4.0 ng/ml, $n = 144$) and intermediate (PSA 4.1–10.0 ng/ml, $n = 611$) PSA groups.

Results: Patients in the low PSA group had significantly smaller prostates ($P = 0.003$) and lower PSA density ($P < 0.001$). The rate of cancer detection was 16.7% (24 of 144) in the low PSA group and 23.7% (145 of 611) in the intermediate PSA group ($P = 0.067$). In men with normal digital rectal examination (DRE), prostate cancer was diagnosed in 14 (13.3%) of the 105 men in the low PSA group and 99 (19.5%) of the 508 men in the intermediate PSA group ($P = 0.139$). In all patients and patients with normal DRE, no statistically significant differences were found in the pathologic findings of biopsy between the two groups.

Conclusions: Our findings provide a rationale to recommend prostate biopsy at lower PSA threshold in this population. At present, however, it is not clear that men who are treated when their cancers are detected at lower PSA levels have better outcomes than those who are treated when the PSA is higher than 4.0 ng/ml.

Key words: prostate-specific antigen – prostate neoplasms – prostate cancer – Asian

INTRODUCTION

Serum prostate-specific antigen (PSA) testing is widely used to screen for prostate cancer. There is general agreement among clinicians that the PSA test has the highest predictive value for prostate cancer, the PSA screening can detect early-stage prostate cancer, and that most cancers detected by PSA screening appear to be clinically important when their pathologic characteristics are used as a surrogate for biological potential (1). However, screening for prostate cancer remains a controversial issue as it has not been proved to reduce disease-specific mortality. In addition, there is disagreement as to what level of PSA should prompt a prostate biopsy although serum PSA levels of greater than 4.0 ng/ml have been considered abnormal over the years.

To date, information on the prevalence of biopsy-detectable prostate cancer among men with PSA values of 4.0 ng/ml or less and no other indication for biopsy (e.g. an abnormal prostate examination) is limited. Furthermore, it is unclear whether the incidence of prostate cancer in Asian men with a lower PSA level is significant. Serum PSA concentration is known to be different across the ethnic groups (2). Thus, a given PSA value may have different clinical meaning for patients of different races. We evaluated the cancer detection rate and the pathologic findings of biopsy in men with PSA levels of 2.0–4.0 ng/ml and those with PSA levels of 4.1–10.0 ng/ml in the Korean population.

PATIENTS AND METHODS

Patients between 45 and 79 years who visited the Department of Urology in three hospitals were entered into a study. We enrolled individuals who visited our department for a variety of reasons including prostate cancer screening and voiding

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symptoms, regardless of whether the visit was primary or referred. All men underwent detailed clinical examinations, including determination of serum levels of total-PSA quantified by immunoradiometric assay (Izotop, Hungary), digital rectal examination (DRE) and transrectal ultrasonography (TRUS). Blood samples were obtained before patients were examined by a physician. All blood was stored at -70°C for less than 1 week, and assayed for serum PSA concentration. Patients with an abnormal DRE and/or serum PSA level greater than 2.0 ng/ml underwent a TRUS-guided needle biopsy by a radiologist after patients provided written informed consent. Transaxial and sagittal scanning of the prostate was performed by a radiologist experienced in this procedure using a 7.0 MHz transducer (Ultramake 9, ATL Inc., Washington, USA). In specimens diagnosed as prostate cancer, additional review was performed on the Gleason score, maximal cancer length, percentage of cancer core (number of cores involved with cancer divided by the total number of biopsy cores), cancer length per biopsy core (total millimeters of cancer in the biopsy specimen divided by the total number of biopsy cores) and percentage of cancer length (total millimeters of cancer in the biopsy specimens divided by total millimeters of biopsy specimens).

Men were excluded from the analysis if they had previously undergone prostate biopsy, had received a prior diagnosis of prostate cancer, had undergone prostate surgery or radiation treatment, had a serum PSA greater than 10 ng/ml or less than 2 ng/ml, had received 5α -reductase inhibitors, had acute urinary retention or an indwelling catheter, had a duration of more than 3 months between PSA measurement and biopsy or with evidence of acute urinary infection (pyuria and bacteriuria) on urinalysis. A total of 755 men met these criteria and constituted the study cohort. In 755 male patients examined, the median age was 65 years (range 40–79). The median prostate volume of the patients was 41.7 cc (range 10–183.6) and their serum PSA ranged from 2 to 10.0 ng/ml (median 5.5).

Values of continuous variables are presented as median (5th–95th percentiles) and rates are expressed as number (%). Patients were divided to low (PSA 2.0–4.0 ng/ml, $n = 144$) and intermediate (PSA 4.1–10.0 ng/ml, $n = 611$) PSA groups. Comparisons of data for serum PSA were made using the χ^2 -test for categorical variables and Mann–Whitney U test for continuous variables. A 5% level of significance was used for all statistical testing and all statistical tests were two-sided. The statistical software package SPSS 10.0 (SPSS, Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Clinical characteristics according to serum PSA are shown in Table 1. Patients in the low PSA group had significantly smaller prostates ($P = 0.003$) and lower PSA density ($P < 0.001$) or PSA density adjusted by transition zone volume ($P < 0.001$). No statistically significant differences in number of cores per biopsy between the two groups but core density (number of cores divided with prostate volume) was higher in

Table 1. Patient characteristics

	PSA 2–4 ng/ml	PSA 4.1–10 ng/ml	<i>P</i> -value
Total patients			
No. patients	144	611	
Age (year)	64 (49–72)	65 (49–74)	0.021
PSA (ng/ml)	3.4 (2.23–4)	6.1 (4.2–9.5)	<0.001
PSAD (ng/ml/cc)	0.09 (0.04–0.17)	0.14 (0.07–0.33)	<0.001
PSATZ (ng/ml/cc)	0.24 (0.07–0.81)	0.32 (0.11–1.11)	<0.001
Total prostate vol (cc)	37 (20.00–72.00)	43 (20.52–91.96)	0.003
Transition zone vol (cc)	14 (4.00–44.00)	19 (5.00–54.15)	0.002
No. abnormal DRE (%)	39 (27.1)	103 (16.9)	0.005
No. cores per biopsy	12 (6.25–13.75)	12 (6–16)	0.983
Core density	0.3 (0.14–0.6)	0.26 (0.11–0.52)	<0.001
No. cancer (%)	24 (16.7)	145 (23.7)	0.067
Patients with normal DRE			
No. patients	105	508	
Age (year)	64 (49–72)	65 (48.45–74)	0.027
PSA (ng/ml)	3.4 (2.23–4)	6.08 (4.2–9.5)	<0.001
PSAD (ng/ml/cc)	0.09 (0.04–0.16)	0.14 (0.07–0.31)	<0.001
PSATZ (ng/ml/cc)	0.23 (0.08–0.82)	0.31 (0.11–1.01)	0.015
Total prostate vol (cc)	37 (20–68.4)	44.7 (21.35–93)	0.005
Transition zone vol (cc)	14 (4–41.75)	21 (6.3–55)	<0.001
No. cores per biopsy	12 (7–14)	12 (6–17)	0.566
Core density	0.36 (0.23–0.71)	0.32 (0.13–0.59)	0.337
No. cancer (%)	14 (13.2)	99 (19.5)	0.139

PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PSATZ, prostate-specific antigen density adjusted by transition zone volume; DRE, digital rectal examination; TRUS, transrectal ultrasonography. Data presented are medians (5th–95th percentiles) or number (%).

the low PSA groups ($P < 0.001$). The rate of cancer detection was 16.7% (24 of 144) when the serum PSA ranged from 2.0 to 4.0 ng/ml and 23.7% (145 of 611) when it was between 4.1 and 10.0 ng/ml ($P = 0.067$). In men with normal DRE, prostate cancer was diagnosed in 14 (13.2%) of the 105 men in the low PSA group and 99 (19.5%) of the 508 men in the intermediate PSA group ($P = 0.139$). At low PSA levels, the cancer detection rate was not significantly different ($P = 0.063$) in patients with (10 of 39, 25.6%) and without (14 of 105, 13.3%) abnormal DRE because of a small number of patients. However, at intermediate PSA levels, the cancer detection rate was significantly higher ($P < 0.001$) in the abnormal DRE group (46 of 103, 44.7%) than in the normal DRE group (99 of 508, 19.5%).

No statistically significant differences were found between the patients with cancer in the low and intermediate PSA groups in Gleason score, number of cancer core, percentage of cancer core, maximal cancer length, total cancer length, cancer length per biopsy core and percentage of cancer length. In men with normal DRE, the biopsy results in patients with

Table 2. Biopsy results of patients with prostate cancer

	PSA 2–4 ng/ml	PSA 4.1–10 ng/ml	P-value
Total patients			
No. patients	24	145	
Gleason score	7 (6–9.75)	6 (6–9)	0.083
No. cancer core	2 (1–12)	2 (1–9)	0.247
No. cancer core per no. total biopsy core (%)	25 (7.69–96.67)	20 (7.69–73–93)	0.471
Maximal cancer length (mm)	3.5 (1–13)	4 (1–12.1)	0.748
Total cancer length (mm)	4.5 (1–81)	8 (1–52.1)	0.925
Total cancer length per no. total biopsy core (mm)	0.38 (0.08–6.75)	0.56 (0.06–4.34)	0.783
Total cancer length per total biopsy core length (%)	20.16 (9.09–63.28)	22.99 (5.56–61.14)	0.843
Patients with normal DRE			
No. patients	14	99	
Gleason score	7 (6–10)	6 (6–8)	0.199
No. cancer core	2 (1–9)	2 (1–9)	0.202
No. cancer core per no. total biopsy core (%)	25 (7.69–75)	16.67 (7.69–83.3)	0.416
Maximal cancer length (mm)	3.5 (2–8)	4 (0.9–12.3)	0.751
Total cancer length (mm)	4.5 (3–39)	7.5 (0.9–71.1)	0.728
Total cancer length per no. total biopsy core (mm)	0.38 (0.23–3)	0.47 (0.05–5.93)	0.674
Total cancer length per total biopsy core length (%)	20.16 (9.09–49.37)	20.81 (5.3–57.81)	0.817

DRE, digital rectal examination.

Data presented are medians (5th–95th percentiles) or number (%).

cancer were not also statistically different between the two groups (Table 2).

DISCUSSION

Our study shows relatively high detection rates of prostate cancer in men with PSA levels between 2.0 and 4.0 ng/ml. Systematic prostate biopsy studies on white and black men with PSA levels between 2.0 and 4.0 ng/ml have demonstrated a cancer detection rate of ~25% (3–6). Recently, Thompson et al. (7) reported the prevalence of prostate cancer among men in the control group of the Prostate Cancer Prevention Trial. During a 7 year period, none of the men in this analysis had PSA levels above 3.0 ng/ml or any abnormality on DRE and all participants underwent a prostate biopsy at the end of the study. Of almost 3000 men in the group, 15% had prostate cancer on the end-of-study biopsy, and of these cancers, 15% were high grade (a Gleason score of 7–9).

In recent studies, at low PSA levels, the cancer detection rate was higher in patients with abnormal DRE than in those with normal DRE although the difference was not significant (8,9). Some authors have reported that DRE has a poor performance in low PSA ranges. Schroder et al. (8) found that the cancer detection rate with DRE alone was 2.5% at PSA levels of 0–3.9 ng/ml. Ohi et al. (9) reported that the cancer detection rate was not significantly different in subjects with (9 of 38, 23.7%) and without (6 of 31, 19.4%) abnormal DRE at PSA levels between 2.1 and 4.0 ng/ml. However, the detection rates

increased dramatically as the PSA level increased to the level of 4.0 ng/ml (10–12). In the study of Bozeman et al. (13), overall positive predictive value of an abnormal DRE was 8.8% but at PSA level 2.0–2.9 and 3.0–3.9 ng/ml, 12.7% and 21.0% of patients were found to have prostate cancer, respectively. Furthermore, Catalona et al. (14) have demonstrated that DRE continued to identify up to 25% of patients with prostate cancer in patients with serum PSA level less than 4.0 ng/ml.

We found no significant differences of the biopsy results between the patients with cancer in the low and intermediate PSA groups. However, some have proposed that low-PSA prostate cancer may be low-volume disease and therefore clinically insignificant. Prostate cancers detected at lower PSA levels are most likely to have a small volume (<0.5 ml) and to be low-grade (15) and are thus more likely to represent clinically insignificant disease. Prostate cancers with a volume of <1 ml do not usually result in PSA levels above 4.0 ng/ml (16). On the contrary, one study showed that the rate of detection of clinically important prostate cancer among men with a PSA level of 2.6–4.0 ng/ml was the same as that among men with PSA values of more than 4.0 ng/ml (17). Catalona and co-workers (4) demonstrated that of cancers detected at serum PSA levels between 2.6 and 4.0 ng/ml, the great majority showed features of medically important tumors. Schroder et al. (10) also asserted that the PSA cut-off level of 4.0 ng/ml would miss large numbers of cancers, and about half of these tumors might have aggressive characteristics and may

still be organ confined. In addition, Recker et al. (18) found 53.8% of the patients with cancer detected within the PSA range 1.0–3.0 ng/ml who underwent radical prostatectomy to have cancer volumes greater than 0.5 cc. Sokoloff et al. (19) also reported that most prostate cancer in men with a PSA level of less than 4.0 ng/ml are clinically significant and many of these tumors are high-grade, high-volume and extraprostatic. A recent study by Punglia et al. (20) used a mathematical method in order to adjust PSA performance for verification bias. This study showed that an important proportion of cancers (82% in men younger than 60 and 65% in older men) were missed if non-adjusted classical PSA values were used as cut-off for prostate biopsy. These authors suggested lowering such a cut-off point to 2.6 ng/ml at least in men under 60 years of age.

Nevertheless, the implications of our results for current recommendations regarding prostate biopsy are unclear. In western countries, the detection rate of prostate cancer by prostate biopsy is more than half in men with PSA levels >10.0 ng/ml, and the likelihood of prostate cancer in men with PSA levels 4.1–10.0 ng/ml (intermediate level) was 22–27% (21). Kobayashi et al. (22) showed that prostate cancer was diagnosed in 23.6% in the low and 23.6% in the intermediate PSA level group. However, the age-specific reference ranges are lower for serum PSA levels and higher for PSA density in Japanese men relative to Caucasian men (23). Improved specificity is important in Asian men with a low PSA level as many do not have prostate cancer. Unless the specificity can be improved, decreasing the PSA threshold may lead to many unnecessary biopsies, as they have inherently lower PSA levels (24,25). In addition, it is still unclear whether the prostate cancer observed in Asian men with lower PSA levels (i.e. <4.0 ng/ml) is significant, which has been reported in both Caucasian and black men.

Several issues of the current study should be mentioned. Our study was not a community-based one. Our aim had not been to estimate the epidemiologic incidence of prostate cancer in men with low PSA levels but to evaluate the rate of prostate cancer detection, in these men, in our daily practice. However, the predictive value of the screening tests may be different in patients presenting with symptoms as opposed to the general population. In addition, it must be recognized that our results relate to a specific group of men, and that different ethnicities may behave somewhat differently because serum PSA levels are race-dependent as well as age-dependent.

In summary, our findings provide a rationale to recommend prostate biopsy at lower PSA threshold in this population. However, lowering the PSA threshold for proceeding to prostate biopsy may increase the risks of overdiagnosing and overtreating clinically unimportant disease as, at present, it is not clear whether men who are treated when their cancers are detected at lower PSA levels have better outcomes than those who are treated when the PSA is higher than 4.0 ng/ml.

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