OBJECTIVE

To identify threshold values of prostate-specific antigen (PSA) levels and PSA velocity (PSAV) to optimize the assessment of the risk of prostate cancer in young men, as prostate cancer is detected increasingly in men aged <50 years.

PATIENTS AND METHODS

Data for a group of 12,078 men, including 1,622 with prostate cancer, were retrieved from the Duke Prostate Center Database. Based on the latest date for a PSA assay, these men were divided into two age groups of <50 and ≥50 years, with 904 and 11,174 men in each group, respectively. Receiver operating characteristic curves (ROC) of PSA and PSAV were calculated and the cancer risk was assessed.

RESULTS

The prevalence of prostate cancer was 4.4% (40 men) for men aged <50 years and 14.2% (1,582 men) for men aged ≥50 years. For the group with cancer the median PSA in men aged <50 years was significantly lower than that in men aged ≥50 (1.3 vs 6.3 ng/mL, P < 0.001). ROC curves of PSA and PSAV showed a breakpoint at a PSA level of 2.3 ng/mL and a PSAV of 0.60 ng/mL/year for men aged <50 years. Both the sensitivity and specificity in the younger group at a PSA level of 2.5 ng/mL were higher than in the older group.

CONCLUSIONS

In men aged <50 years the operating characteristics of PSA are more sensitive and specific than in older men. Diagnostic PSA levels in men aged <50 years are significantly lower than suggested by guidelines. Using a 2.0–2.5 ng/mL PSA level threshold for biopsy in men aged <50 years and a PSAV threshold lower than the traditional 0.75 ng/mL/year is reasonable in contemporary practice. Further studies are warranted to validate these thresholds.

KEYWORDS

PSA velocity, age-adjusted PSA levels, sensitivity, specificity
testing the median age of diagnosis has decreased substantially and it has been confirmed that being younger at diagnosis is an independent predictor of a better prognosis [2,3]. While as few as 25% of men with a PSA level of 4–10 ng/mL have prostate cancer, up to 25% of men with a PSA of <4 ng/mL will have prostate cancer [4–6]. This poor specificity prompted the introduction of age-adjusted PSA level thresholds [7]. Younger men have lower PSA values, prompting some, e.g. Oesterling et al. [7] and Moul et al. [8], to suggest that the upper limit of normal PSA in men aged 40–49 years is 2.5 and 2.0 ng/mL, respectively.

Smith and Catalona [9] showed that the vast majority of tumours detected through PSA screening are clinically significant. Clinically significant prostate cancer implies that the treatment of these tumours will directly affect either the quality or length of the patient’s life. The question of clinically significant cancer is usually an issue in older patients, as many die from causes unrelated to their prostate cancer. This has led us and others to hypothesise that lowering PSA level thresholds in men aged <50 years would result in increased detection and treatment of early-stage prostate cancer that would potentially affect the length of their lives. Furthermore, as the incidence of BPH increases from 9% in men aged <60 years to 17% in men aged >60, screening younger men should result in fewer false-positive results [10].

The objective of the present study was to identify PSA kinetic data and optimized screening variables that could be used to recognize clinically significant prostate cancer in young men.

**PATIENTS AND METHODS**

A group of 12 078 men (aged 40–96 years) with at least two PSA tests within a 2-year period were retrieved from the Duke Prostate Center outcomes database, that contains data for >14 000 patients with prostate cancer and >1.5 million associated clinical records; 904 of these men were aged <50 years and 12 074 were aged ≥50 years. For the group with prostate cancer, PSA values drawn within 2 years before the first positive biopsy were included. Patients with either a negative biopsy or no known history of prostate cancer were included in the no-cancer arm. It was important to include these patients, as their PSA values and velocities served as the controls for the patients who had positive biopsies. PSA velocity (PSAV) was calculated as the slope of the linear regression line of all PSA values over time [5]. All PSA values after diagnosis were excluded from the dataset, as were all men who did not have at least two PSA values within 2 years and were not aged ≥40 years. Men were stratified into two age groups, i.e. <50 and ≥50 years, based on their age at the time of the most recent PSA test.

Receiver operating characteristic (ROC) curves were calculated and used to analyse the sensitivity and specificity of PSA and PSAV for detecting prostate cancer in men aged <50 and ≥50 years. The ROC curve break-points served to establish the new PSA level and PSAV thresholds for young men. The positive predictive value (PPV) was calculated by dividing the number of cancers detected by the number of all men meeting the criteria being evaluated. Finally, we compared the number of cancers detected between the old and new criteria.

Results were considered statistically significant with a two-sided α of <0.05. The Mann–Whitney U-test was used to determine P values, as the data had a non-Gaussian distribution. Chi-square tests were used to evaluate the racial composition of each cohort and the percentiles.

**RESULTS**

Among the 12 078 men in the study, 1622 (13.9%) were diagnosed with prostate cancer by prostatic needle biopsy. Of the 904 men aged <50 years, 40 were diagnosed with cancer (4.4%), with a median age of 48.1 years. Of these men, four had a family history of prostate cancer and six had an abnormal DRE. The distribution of race in the groups with cancer aged <50 and ≥50 years were similar (Table 1).

The median age at last PSA sampling was substantially younger for those aged ≥50 and with no cancer than for those with cancer (66 vs 69 years). This was also the trend in men aged <50 years with no cancer, with a median age of 46, vs 48 years in the group with cancer (Table 1).

For men aged ≥50 years and no cancer the median PSA and PSAV were 5.1 ng/mL and 0.25 ng/mL/year, respectively, vs 6.3 ng/mL
TABLE 2 The sensitivity and specificity of PSA level and PSAV between the age groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;50 years</th>
<th>&gt;50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA level, ng/mL</td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
</tr>
<tr>
<td>1.0</td>
<td>85.0</td>
<td>73.6</td>
</tr>
<tr>
<td>2.0</td>
<td>75.0</td>
<td>92.2</td>
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<tr>
<td>2.5</td>
<td>73.8</td>
<td>94.1</td>
</tr>
<tr>
<td>3.0</td>
<td>68.8</td>
<td>95.9</td>
</tr>
<tr>
<td>4.0</td>
<td>61.3</td>
<td>97.7</td>
</tr>
<tr>
<td>PSAV, ng/mL/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.10</td>
<td>95.2</td>
<td>41.0</td>
</tr>
<tr>
<td>0.20</td>
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<tr>
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</tr>
<tr>
<td>0.75</td>
<td>66.7</td>
<td>86.3</td>
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</tbody>
</table>

FIG. 1. PSA level (left) and PSAV (right) were better predictors of prostate cancer in young men.
a PPV of 18.1% for a PSAV of ≥0.60 ng/mL/year and PPV of 36.6% for a PSA level of ≥2.5 ng/mL (Table 3). However, only one additional man with cancer was detected using the new PSAV criteria, compared with the traditional one.

DISCUSSION

Recent work has cast doubt on the existence of a true PSA level threshold for biopsy [11]. Others have indicated that many men with cancer actually have PSA values of <4.0 ng/mL [6]. Regardless of the current views questioning the validity of PSA, its impact is undeniable [3,12]. PSA remains the best prostate cancer-screening tool currently available, and the standard against which all others are judged. As the ‘baby-boom’ generation reaches its peak years for prostate cancer it is imperative that urologists use PSA judiciously and effectively to minimize the economic impact on an already overburdened healthcare system, and maximize its effectiveness to detect and treat early-stage and clinically significant prostate cancer. In the present study we explored whether lowering the current PSA level threshold and using PSA kinetics at 40 years instead of 50 years old would lead to the detection of more curable prostate cancer.

There are three main reasons that make PSA screening with a lowered threshold useful in men aged 40–49 years. First, the incidence of BPH is lower in young men [4]. Second, PSA screening in younger men is more likely to detect men with curable, clinically localized cancer. Finally, younger men are less likely to have significant medical comorbidities and more likely to opt for definitive treatments such as surgery.

Currently, there are few data on PSA screening in men aged <50 years. The idea of lowering the PSA level threshold was explored previously, Oesterling et al. [11] proposed age-specific PSA level thresholds for men aged 40–49 years of 2.5 ng/mL for Caucasians and 2.0 ng/mL for African-Americans. Many others suggested that lowering the PSA level threshold for biopsy, in addition to lowering the screening age, might be advantageous [2,3,6,13]. Although PSA should be viewed as a continuum on which to judge prostate cancer [10], most urologists still rely on firm thresholds or a reasonable range for PSA screening.

Using the ROC curves to examine PSA level and PSAV in men aged <50 years, it is clear that although the area under the curve was higher for this cohort, the traditional thresholds for cancer biopsy are inadequate and miss a significant proportion of men with cancer (Fig. 1 and Table 2). Further, there is a breakpoint in the curve at 2.3 ng/mL, indicating that that 2.0–2.5 ng/mL for PSA in this age group would be more reasonable, as this PSA value maximizes the sensitivity and specificity in men aged <50 years and detected an additional five (12.5%) with cancer, whereas the PSAV value only detected one additional man with cancer (Fig. 1 and Table 2).

The data used in the present study were from Duke Urology clinic, rather than from a ‘pure’ population-based study. Interestingly, the median PSAV for men aged <50 years with cancer was 1.83 ng/mL/year, well above the traditional PSAV threshold and similar to that of men aged ≥50 year (1.78 ng/mL/year) but the breakpoint in the ROC curve was 0.60 ng/mL/year. The high median PSAV suggests that current PSAV thresholds might be adequate or that we have a selection bias toward men with aggressive prostate cancer in this population not regularly subjected to PSA screening, and are probably missing men with less advanced disease. To characterize PSAV kinetics, the study included men with two or more PSA estimates, without counting the men with one PSA value and diagnosed with prostate cancer (hence, PSAV >0). These limitations could affect the ability to generalize these findings to the overall population. Information from a DRE and the family history in men aged ≥50 years was unavailable. This information is vital to future studies, as it is likely that most men aged <50 years diagnosed with prostate cancer were initially detected by a DRE. Thus, by examining only this cohort of men the data might be skewed towards young men with more aggressive cancer.

Further, the new thresholds significantly decreased the PPV from 20% to 18.1% for PSAV, and 54.3% to 36.6% for PSA. This suggests that in the future an optimized PSAV threshold could provide a better screening tool than simply lowering the PSA level threshold, as it does not lower the PPV as much, but further studies with larger groups of men with prostate cancer and aged <50 years are needed to define the role of PSAV in this cohort.

In conclusion, PSA level and PSAV patterns in men aged <50 years are different from those in men aged ≥50 years. Diagnostic PSA levels in men aged <50 are much lower than the guidelines suggested by the AUA. Using a PSA level threshold of 2.0–2.5 ng/mL for biopsy in men aged <50 years is advised, as is lowering the PSAV threshold to ≤0.60 ng/mL/year in this group. Further studies on men aged <50 years are warranted to validate the thresholds and ranges proposed.

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CONFLICT OF INTEREST

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Abbreviations: PSAV, PSA velocity; PPV, positive predictive value; ROC, receiver operating characteristic (curve).