Distribution of prostate specific antigen (PSA) and percentage free PSA in a contemporary screening cohort with no evidence of prostate cancer

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OBJECTIVE

To explore the distribution of total prostate specific antigen (PSA) and percentage free/total PSA (%f/tPSA) in healthy volunteers with no clinical evidence of prostate cancer, who participated in prostate cancer screening.

SUBJECTS AND METHODS

PSA and %f/tPSA values from 2323 men, who participated in one of three annual prostate cancer screening events between 2004 and 2006, were tabulated according to age strata of 40–49, 50–59, 60–69 and 70–79 years. Local regression smoothing plots provided a graphical display of the relation between age and PSA or %f/tPSA, respectively. All PSA and %f/tPSA analyses were repeated for each age category after excluding, respectively, the top and the bottom 10% of PSA and %f/tPSA values.

RESULTS

Within the entire cohort, the median PSA level was 1.0 ng/mL and the median %f/tPSA was 25%. According to the age categories the PSA level and %f/tPSA medians within the entire cohort were, respectively, 0.7, 0.9, 1.3, 1.8 ng/mL and 28.0, 26.0, 24.0 and 25.0%. Of the 2323 men, 438 (18.9%) had a PSA level of >2.5 ng/mL and 1172 (50.5%) had a %f/tPSA of ≤25%. When either a PSA level of >2.5 ng/mL or a %f/tPSA of ≤25% were considered, 1235 (53.2%) had one or two abnormal values. Finally, if either a PSA level of >2.5 ng/mL or %f/tPSA of ≤15% was used, 617 (26.6%) were considered abnormal.

CONCLUSION

Half of men with no clinical evidence of prostate cancer should have PSA levels of <1.0 ng/mL and a %f/tPSA of >25%. A PSA level threshold of 2.5 ng/mL would require a biopsy in 20% of men and a %f/tPSA threshold of ≤25% in half of the men. Alternatively, a %f/tPSA threshold of ≤15% would decrease the probability to 15%.

KEYWORDS

prostate cancer, PSA, % free PSA, screening, detection, biopsy

INTRODUCTION

Controversy surrounds the definition of a ‘normal’ serum PSA level [1–9]; the status quo of ‘normal’ values was recently questioned by the Prostate Cancer Prevention Trial (PCPT) trial data [9], where a large proportion of men with PSA level of <2.5 ng/mL were found to have prostate cancer. Before this study the accepted ‘normal’ PSA threshold was progressively lowered from 4.0 to 2.5 ng/mL [10,11]. Recently, several investigators reported even lower PSA distributions in several screening cohorts [3–13], e.g. Thompson et al. [9] detected prostate cancer in 15.2% of men whose total PSA level was <4.0 ng/mL. Despite very low PSA levels of 0.1–1.0 ng/mL, up to 16.7% of those men had prostate cancer on biopsy. Moreover, Fang et al. [5] showed, in the Baltimore Longitudinal Study of Aging, with a follow-up spanning three decades, that a PSA level above the median for age groups 40–49 and 50–59 years increased the risk of prostate cancer, respectively, by 3.6 and 3.5 times. Also, Loeb et al. [12] reported that men in a screening cohort aged <60 years and with baseline PSA levels of 0.6–2.5 ng/mL are at greater risk of having unfavourable prostate cancer (P<0.0001) than men with a baseline PSA level of <0.6 ng/mL. Finally, the same group also showed that a baseline PSA level between the age-adjusted (40–49, 50–59, >60 years) median PSA values (0.7, 0.9, 1.4 ng/mL) and 2.5 ng/mL represents a significant risk factor (P<0.001) for developing prostate cancer. Men aged 40–49 and 50–59 years had, respectively, 14.6 and 7.6 times the risk of prostate cancer than men with a baseline PSA equal or below the median [13]. These data question the established definitions of what constitutes a ‘normal’ PSA level, i.e. a range of values that reflect the distribution seen in men with no evidence of prostate cancer [9,12–14]. Based on the lack of established ‘normal’ definitions, we assessed the distribution of total PSA and percentage of free/total PSA (%f/tPSA) values...
in a large screening cohort of healthy men with no diagnosis of prostate cancer.

SUBJECTS AND METHODS

The study group consisted of 2323 men with no known prostate cancer who participated in one of three annual prostate cancer-screening events, the Prostate Cancer Awareness Days in 2004-2006. The events are organized by a multidisciplinary group of urologists, oncologists, radiation oncologists, nurses, support group members and nutrition experts from the University of Montreal Health Center. The aim of the event is to educate, inform and raise public awareness about prostate cancer. None of the men included participated in more than one annual screening event. There were no duplicate entries and only men aged 40–79 years were invited. The Hybritech (Beckmann-Coulter, Inc., Canada) assay was used for both PSA and %f/tPSA measurements.

PSA level and %f/tPSA distributions were explored and tabulated for the entire cohort, and according to age strata of 40–49, 50–59, 60–69 and 70–79 years. Moreover, we used local regression smoothing plots with the intent of providing a graphical display of the relation between age and PSA. This technique represents a generalization of running means, which derive a predicted value at each point by fitting a weighted linear regression, where the weights decrease with distance from the point of interest. Connecting these predicted values produces a smooth curve. It is less sensitive to influential outliers and extremes than linear regression.

All analyses were repeated after excluding men with PSA levels in the top 10% of the PSA distribution, which was termed the truncated PSA cohort. Similarly, all %f/tPSA analyses were repeated after excluding men with %f/tPSA values in the bottom 10% of the distribution, termed the truncated %f/tPSA cohort. The intent of restricting the cohort to 90% of men within the lower PSA distribution or upper 90% of the %f/tPSA distribution was dictated by the possibility of occult prostate cancer within those strata. Our intent was to exclude these patients from the analysis of normal PSA and %f/tPSA values. Moreover, according to Eastham et al. [15], a proportion of men with a high serum PSA level might have a transient PSA increase or an increase unrelated to prostate cancer. All tests were two-sided with a significance level set at \( P < 0.05 \).

RESULTS

The median (mean, range) age of the 2323 study participants was 58 (58.3, 40–79) years; Table 1 shows the descriptive characteristics of the 2323 men and the truncated PSA (2090) and %f/tPSA (2095) groups. Of all men, 459 (19.8%), 882 (38.0%), 634 (27.2%) and 348 (15.0%) were aged 40–49, 50–59, 60–69 and 70–79 years. In the entire cohort, the mean (median, range) PSA level was 1.8 (1.0, 0.1–47.3) ng/mL and the %f/tPSA levels 26.8 (25.0, 3–83).

Within the truncated PSA group, the mean (median, range) PSA level was 1.2 (0.9, 0.1–3.9) ng/mL and in the truncated %f/tPSA group the %f/tPSA was 28.6 (27.0, 14–83). Of the entire cohort, 438 men (18.9%) had a PSA level of \( >2.5 \) ng/mL and 226 (9.7%) of \( \geq 4.0 \) ng/mL; 1172 (50.5%) had a %f/tPSA of \( \leq 25 \) and 345 (14.9%) a %f/tPSA of \( \leq 15 \). The stratification of these values according to age is shown in Table 1.

The truncated PSA (lower 90%) distribution according to age is shown in Fig. 1a; in this group the upper 95% CI for PSA was 3.0 ng/mL; the upper 95% CI for PSA according to age categories 40–49, 50–59, 60–69, 70–79 years, were, respectively, 2.1, 2.7, 3.3 and 3.4 ng/mL. The loess curve that fitted 99% of the observations shows that PSA changed substantially with increasing age. The central PSA values for each age-specific loess segment were 0.7, 0.8, 1.1 and 1.4 ng/mL, respectively.

The truncated %f/tPSA (upper 90%) distribution according to age is shown in Fig. 1b; in this group the lower 95% CI was 15% and the lower 95% CI according to age categories 40–49, 50–59, 60–69, 70–79 years were, respectively, 16.0, 15.7, 15.0 and 15.0%. The loess curve fitting 99% of the observations showed that %f/tPSA is less affected by age than PSA. The central %f/tPSA values for each age-specific loess segment were 29.0, 27.0, 25.0 and 25.5%, respectively.

DISCUSSION

In the present era of predominantly impalpable prostate cancer, PSA represents the main indicator of the likelihood of harbouring prostate cancer. However, the best threshold value has been disputed and revised by several investigators [1–13]. Some showed an identical prostate cancer detection rate for PSA levels of 2.5–4 ng/mL vs 4–10 ng/mL [10,11]. However, a universal threshold might not apply to all men [6–8]. Therefore, efforts were made to improve the sensitivity and specificity of PSA [16–18]. For example, a cohort of 471 men with no evidence of prostate cancer was used earlier to define age-specific PSA reference ranges [16]. These reference ranges were subsequently revisited and adjusted for race by Morgan et al. [17]. However, comparing these values with more recent data from a large group of 2950 men with no clinical evidence of prostate cancer cast doubt on the validity of these age-specific threshold. Also, to the best of our knowledge, the contemporary relationship between PSA and age was not tested previously [9]. Furthermore, few if any investigators...
addressed the distribution of %f/tPSA in contemporary men with no known prostate cancer. In 1995, Oesterling et al. [18] suggested that %f/tPSA does not depend on the subjects’ age. Moreover, they suggested that the ideal normal threshold would be 15%. Based on the controversy about ‘normal’ PSA values and based on almost no data for the %f/tPSA distribution in men with no prostate cancer, we explored the distribution of these two markers in a large and contemporary screening cohort that was accrued over 3 years.

Our data showed that half the men has a PSA level of ≤1.0 ng/mL and that 90% had a PSA level of <4 ng/mL. If a PSA threshold of 2.5 ng/mL is used, then 81.1% of men were below that threshold. Within the truncated PSA cohort, where only the lower 90% of the distribution was used, the upper bound was 3.9 ng/mL. The median of the entire cohort was 1.0, and was 0.7, 0.9, 1.3 and 1.8 for age strata 40–49, 50–59, 60–69 and 70–79 years. Taken together, these PSA data show that most men should have very low PSA levels, which are mostly <1.0 ng/mL; >80% of men should have PSA levels of 0–2.5 ng/mL. Finally, the PSA central tendencies vary with age, but substantially less than was shown by Oesterling et al. in 1995 [18]. These findings agree closely with tendencies reported recently by others [5,9,13]. Conversely, our findings disagree with historic observations made by others [16–18], where substantially higher central tendencies were recorded.

We repeated the assessment of PSA distribution in a subset of men where the top 10% of PSA and %f/tPSA was excluded. The results are presented in Table 1.

Table 1: Descriptive characteristics, PSA and %f/tPSA distribution of 2323 men with no evidence of prostate cancer according to age categories, and after excluding, respectively, the top and the bottom 10% of PSA (2090) and %f/tPSA (2095)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age groups, years</th>
<th>Entire cohort</th>
<th>Truncated (top 10%) PSA group</th>
<th>Truncated (bottom 10%) %f/tPSA group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, (%)</td>
<td>2323 (100)</td>
<td>2090 (100)</td>
<td>2095 (100)</td>
<td>2095 (100)</td>
</tr>
<tr>
<td>PSA level ≤4.0 ng/mL</td>
<td>226 (9.7)</td>
<td>205 (9.8)</td>
<td>944 (45.1)</td>
<td>944 (45.1)</td>
</tr>
<tr>
<td>PSA level &gt;2.5 ng/mL</td>
<td>438 (18.9)</td>
<td>205 (9.8)</td>
<td>205 (9.8)</td>
<td>205 (9.8)</td>
</tr>
<tr>
<td>%f/tPSA ≤25%</td>
<td>1172 (50.5)</td>
<td>258 (25.0)</td>
<td>258 (25.0)</td>
<td>258 (25.0)</td>
</tr>
<tr>
<td>%f/tPSA ≤15%</td>
<td>345 (14.9)</td>
<td>15 (0.9)</td>
<td>15 (0.9)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>Mean (median) PSA, ng/mL</td>
<td>1.8 (1.0)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>Mean (median) %f/tPSA</td>
<td>26.8 (25.0)</td>
<td>28.9 (28.0)</td>
<td>28.9 (28.0)</td>
<td>28.9 (28.0)</td>
</tr>
<tr>
<td>Upper 90% PSA, ng/mL</td>
<td>4.0</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Central PSA age category loess tendency, ng/mL</td>
<td>0.1–7.3</td>
<td>0.1–5.6</td>
<td>0.1–5.6</td>
<td>0.1–5.6</td>
</tr>
<tr>
<td>Lower 90% of %f/tPSA, %</td>
<td>1.0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Central %f/tPSA age category loess tendency, %</td>
<td>25.0</td>
<td>28.0</td>
<td>28.0</td>
<td>28.0</td>
</tr>
</tbody>
</table>

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10% of all values were removed. The objective of this restriction was to exclude the possibility of occult prostate cancer in some screening participants. Moreover, according to Eastham et al. [15], a proportion of men with a high serum PSA level might be having a transient PSA increase or an increase unrelated to prostate cancer.

Reassessing the central tendencies in the truncated PSA cohort (2090 men) showed an overall PSA median of 0.9 ng/mL and age-stratified medians of 0.7, 0.8, 1.1 and 1.4 ng/mL. The upper limits of the 95% distribution in the truncated cohort were 3.0 overall, and 2.1, 2.7, 3.3 and 3.4 ng/mL for age categories 40–49, 50–59, 60–69 and 70–79 years, respectively. The central values of the loess curve, for age strata 40–49, 50–59, 60–69 and 70–79 years were, respectively, 0.7, 0.8, 1.1 and 1.4 ng/mL. These findings paralleled the median values. The agreement between the full and the restricted analyses reinforced the notion that most men should have PSA level of 0.6–1.1 ng/mL, and that age has a not insignificant effect on PSA distribution [5,9,13]. Nonetheless, in the entire cohort, 18.9% of men had PSA levels of >2.5 ng/mL. This proportion decreased to 9.8% in the restricted cohort. Our findings suggest that age-adjusted median PSA values might be more appropriate than a value that is defined regardless of age.

Our data showed that 50.5% of men (1172) had %f/tPSA values of <25%; the age-stratified %f/tPSA medians were, respectively, 28.0, 26.0, 24.0 and 25.0% (Table 1). In the truncated %f/tPSA cohort (2095 men), 45.1% still had %f/tPSA values of <25%. Reassessing the central tendencies in the truncated group showed an overall median of 27.0% and age-stratified medians of 29.0, 27.0, 25.0 and 25.5%, for age strata 40–49, 50–59, 60–69 and 70–79, respectively. The lower limit of the 95% distribution in the truncated cohort was 15%. Age-specific lower 95% limits were, respectively, 16.0, 15.7, 15.0 and 15.0% for age categories 40–49, 50–59, 60–69 and 70–79. The central values of the loess curve, for age strata 40–49, 50–59, 60–69 and 70–79 were, respectively, 29.0, 27.0, 25.0 and 25.5%. These findings replicate the median values. Based on the %f/tPSA distribution it might be difficult to justify a 25% threshold for %f/tPSA, as this would require a biopsy in half the men. Conversely, a %f/tPSA threshold of 15% would imply that 14.9% would need a biopsy.

The present study has several limitations, the most important being that biopsies were not taken as part of the screening initiative. Therefore, men with ‘normal’ PSA level might have harboured prostate cancer. Thompson et al. [9] showed that 15.2% (449) men with a PSA level of <4 ng/mL and with a normal DRE had prostate cancer, with an even distribution across the age groups. The PCPT data showed that of all men with prostate cancer, 337 (67.8%) had PSA level above the mean PSA of 1.34 ng/mL. Similar findings were reported by Loeb et al. [13] in a large screening population of 14,000 men aged <60 years. They suggested that a PSA level of <2.5 ng/mL but above the population median (0.7 ng/mL in men in their fifth decade, and 0.9 ng/mL in the sixth), represents a significant risk factor (P<0.001) for developing prostate cancer. Men aged 40–49 and 50–59 years with PSA level of <2.5 ng/mL and above the median had, respectively, a 15-fold and an eight-fold increase in prostate cancer risk. Based on these findings, a proportion of men within the present cohort had prostate cancer; unfortunately, the exact number is unknown. Similarly, the characteristics of cancers that are undiagnosed in the present population of men with low PSA levels are unknown; possibly some might be indolent, but others might be aggressive [19].

The lack of detection of prostate cancer in men with a PSA level below the threshold, which is considered abnormal, represents a limitation of any study driven by PSA thresholds. Unfortunately, it is difficult to justify a biopsy in all men regardless of PSA threshold. Such an approach was used in one study and provided valuable information about the prostate cancer distribution within normal PSA values. The lack of consideration of the DRE findings represents a design limitation of the present study. However, it might be postulated that a suspicious DRE will be found in a negligible proportion of men, especially with low PSA levels [9]. Finally, we did not adjust for the effect of race, as virtually all the participants were Caucasian. There might also be a ‘volunteer bias’, as men who volunteer to participate in a health initiative are usually more health-conscious than those who do not. Despite these limitations, our data represent a useful reference of what the PSA level and %f/tPSA distribution might be in men with no clinical evidence of prostate cancer.

In conclusion, half of men with no clinical evidence of prostate cancer should have PSA levels of <1.0 ng/mL and a %f/tPSA of >25%. A PSA threshold of 2.5 ng/mL would require biopsy in 20% of men, and a %f/tPSA threshold of <25% in half of men; a %f/tPSA threshold of ≤15% would decrease the probability to 15%.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: PCPT, Prostate Cancer Prevention Trial; %f/tPSA, percentage of free/total PSA.