Screening for prostate cancer in a city in Japan: Age-specific prostate-specific antigen cutoff thresholds

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Abstract

Purpose:
Older men have higher prostate-specific antigen levels than younger men. However, the current Japanese Urological Association guidelines recommend secondary screening at a cutoff value of 4.0 ng/mL, even in older men. Here, we reexamined the cutoffs for older men using a prostate screening cohort in Japan, and first performed an analysis to determine the indication cutoffs for detecting positive biopsies.

Methods:
Data from 68,566 prostate cancer screenings in the city in 2018 were combined with cancer registration data. The optimal prostate-specific antigen levels to predict prostate cancer in different age groups were calculated using receiver operating characteristic curves after determining whether a cancer was registered within one year of screening.

Results:
At the conventional prostate-specific antigen threshold of 4.0 ng/mL, the sensitivity, specificity, and negative predictive value were 94.9%, 91.7%, and 91.7%, respectively. The optimal prostate-specific antigen cutoff values for patients aged 50–59 years, 60–69 years, 70–79 years, and over 80 years were 3.900 ng/mL, 4.014 ng/mL, 4.080 ng/mL, and 4.780 ng/mL, respectively.

Conclusions:
The sensitivity and specificity of prostate cancer screening in the city were high, indicating a highly accurate screening. The prostate-specific antigen threshold was 4.78 ng/mL in patients older than 80 years. A higher prostate-specific antigen threshold may be useful in men over 80 years to avoid excess biopsy and reduce costs. Our results suggest that the Japanese current method of using PSA 4.0 ng/mL as a cutoff regardless of age may not be preferable in the older men.

Introduction
Prostate-specific antigen (PSA) was approved as a marker for prostate cancer screening by the US Food and Drug Administration in 1994.[1] In Japan PSA screening is not a public countermeasure type screening of the country, but many local governments are conducting PSA screening as a countermeasure-type screening. PSA screening can reduce prostate cancer-related mortality in men aged 55 to 69 years,[2] but evidence for a mortality-reducing effect is still controversial at this time. PSA screening has not been shown to reduce mortality in men aged 70 and over. The effect of PSA screening on reducing the mortality rate is limited, but some local governments are conducting PSA screening as a
countermeasure-type screening regardless of age. Although public health questions remain, as long as it is actually being carried out, it should be evaluated.

Older men have higher PSA levels than younger men.[3–5] Although PSA has high sensitivity and specificity, indicating its high accuracy in detecting prostate cancer, there are problems such as overdiagnosis, especially in older men. However, the current system recommended in the JUA guidelines is designed to recommend secondary screening at a cutoff 4.0 ng/mL, even for those who are older.

An age-specific PSA threshold is a reasonable concept and could reduce screening costs and the likelihood of overdetection and false-positive PSA test results. Several studies have estimated age-specific PSA reference ranges.[3, 4, 6] In particular, a prostate cancer screening study using age-specific PSA cutoff values in Japan[6] suggested their potential usefulness. The report suggested that the PSA cutoff threshold might be lower than that recommended in the Japanese Urological Association (JUA) guidelines, and use of this lower threshold could reduce cancer oversight. In the JUA guidelines for prostate cancer, PSA cutoffs for biopsy indications are set at 3.0 ng/mL, 3.5 ng/mL, and 4.0 ng/mL for patients aged 50–64 years, 65–69 years, and ≥ 70 years, respectively, based on clinical evidence from a Japanese population screening cohort in the 1990s.[7] The JUA cutoff value is the same for those aged 70 years and over, regardless of age. Ito et al. reported that the threshold in the over 80-year group was higher than 4.0 ng/dl, but the number of patients in the group at that time was small, so it was not adopted as the threshold for JUA. Therefore, it may be necessary to consider elderly patients in an aging society with respect to PSA cutoffs. However, Gilbert et al.[8] reported that there is no benefit to using the age-specific thresholds suggested by the National Institute of Clinical Excellence guidelines because the detection of high-risk prostate cancer is reduced using the age-specific thresholds, although the PSA threshold in the control group was 3.0 ng/mL, which is low. In view of the longevity of the elderly, biopsies and therapeutic interventions should be conducted with caution. To avoid excessive biopsies, we reexamined the cutoffs for the elderly using real-world data from the city, and first performed an analysis to determine the indication cutoffs for detecting positive biopsies.

We hypothesized that a higher PSA threshold would be identified for older men, and use of this threshold could reduce the number of unnecessary biopsies in patients with benign disease. We also hypothesized that we would identify a lower threshold for younger men, and use of this threshold could reduce the rate of missed prostate cancers. The present study is the first in Japan using large-scale, real-world data to evaluate the confirmation of quality control indicators for each age group using real-world data in a city in Japan.

Methods

Prostate cancer screening in the city

The city is a large city in Kanagawa prefecture. Prostate cancer screening in Japan is not administered nationally as a countermeasure-type screening but is determined individually by each local government.
The city conducts PSA countermeasure-type examinations. Men over the age of 50 can receive a PSA screening at a low cost. In this system, a PSA level over 4.0 ng/mL is considered positive. Men with a positive prostate cancer screening result undergo a medical examination at the Department of Urology as a secondary screening. In the secondary screening, MRI imaging, PSA re-examination, digital rectal examination, are performed to determine the indication of biopsy. Prostate cancer screening data include age, screening date, PSA value, a positive test result, and place of residence.

Patients

We used the population-based cancer registry data for the Kanagawa prefecture (known as the Kanagawa Cancer Registry[9]). All data from the Kanagawa Cancer Registry were retrieved and anonymized from the database after obtaining permission from the Kanagawa prefecture. The information of Kanagawa Cancer Registry is available on the Kanagawa Prefectural Government website (https://www.pref.kanagawa.jp/docs/nf5/ganntaisaku/know-about-gan/ganntouroku.html). We retrieved data from patients who underwent PSA screening in the city between January and December 2018. The PSA screening data were evaluated against the prostate cancer (PCa) registration data from the Kanagawa Cancer Registry. Since registration data does not collect common numbers, matching is performed independently based on personal information. Those with an ICD-10 code of C61 in the Cancer Registry were considered positive. If the patient had a check-up in the next year within 365 days, we confirmed the cancer registry up to that check-up date. This study was approved by the Institutional Review Board of Kanagawa Cancer Center (Epidemiology-78).

Statistical analysis

Contingency tables were used to estimate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio of the conventional screening methods. Those who were diagnosed with PCa within one year after undergoing screening and registered for PCa were regarded as PCa positive. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal PSA cutoff for each age group (50–59 years, 60–69 years, 70–79 years, and ≥ 80 years). In addition, ROC curves were created for the 50–64 year, 65–69 year, and over 70–year age groups, which are those used in the JUA guidelines. The point of the ROC curve closest to the top left was used as the threshold. We used EZR version 1.54[10] to perform the ROC analysis. EZR is an R-based software developed by Saitama Medical Center.

Results

Screening cohort and patient characteristics

A total of 68,566 men underwent prostate cancer screening in the city in 2018. The screening rates for men aged 50–59 years, 60–69 years, 70–79 years, and over 80 years were 3.12%, 9.23%, 15.64%, and 10.66%, respectively. There were 8,439, 19,944, 29,347, and 10,837 men in the 50–59 year, 60–69 year, 70–79 year, and over 80–year groups, respectively. The PSA screening data were evaluated against the
data of the Kanagawa Cancer Registry. There were 768 men with prostate cancer in the registry, and 729 cancers were detected by the PSA screening. The median age of the cancer patients was 71.0 years.

**Screening accuracy**

The contingency table is shown in Table 1. We first evaluated the accuracy of the conventional PSA threshold (4.0 ng/mL). At this cutoff threshold, the sensitivity was 94.9%, the specificity was 91.7%, the PPV was 11.4%, the NPV was 91.7%, the positive likelihood ratio was 11.4, and the negative likelihood ratio was 0.06. The sensitivity and specificity of the conventional threshold in each age group are shown in Fig. 1. In the 50–59 year group, the sensitivity was 95.8% and the specificity was 96.7%; and they were 95.1% and 93.4%, respectively, in the group aged 60–69 years. The sensitivity and specificity were 95.1% and 91.0% respectively in the group aged 70–79 years; and they were 93.7% and 86.2%, respectively, in the group aged over 80 years. In comparison with the other groups, the group over 80 years had a lower sensitivity and specificity.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>PCa</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>729</td>
<td>5661</td>
</tr>
<tr>
<td>Negative</td>
<td>39</td>
<td>62137</td>
</tr>
<tr>
<td>total</td>
<td>768</td>
<td>67798</td>
</tr>
</tbody>
</table>

incidence 1.1%  sensitivity 94.9%  specificity 91.7%

Positive predictive value 11.4%  Negative predictive value 99.9%

Positive likelihood ratio 11.4  Negative likelihood ratio 0.06

PSA cut-off of the screening is 4.0ng/ml

PCa: prostate cancer; PSA: prostate specific antigen

Table 2 shows the screening accuracy summary of our study and that of 14 other studies reported by Merriel et al.[25] with a PSA of 4 ng/mL or higher as a cutoff. The sensitivity in this study was comparable to those of past reports,[11–24] but the specificity was higher.
Table 2
Diagnostic accuracy of PSA ≥ 4.0 ng/mL for prostate cancer detection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdrabo[11]</td>
<td>2011</td>
<td>0.92</td>
<td>0.24</td>
<td>0.35</td>
<td>0.87</td>
</tr>
<tr>
<td>Agnihotri[12]</td>
<td>2014</td>
<td>0.99</td>
<td>0.05</td>
<td>0.59</td>
<td>0.80</td>
</tr>
<tr>
<td>Aragona[13]</td>
<td>2005</td>
<td>0.92</td>
<td>0.15</td>
<td>0.38</td>
<td>0.76</td>
</tr>
<tr>
<td>Chang[14]</td>
<td>2015</td>
<td>0.89</td>
<td>0.09</td>
<td>0.19</td>
<td>0.76</td>
</tr>
<tr>
<td>Chavan[15]</td>
<td>2009</td>
<td>0.96</td>
<td>0.03</td>
<td>0.18</td>
<td>0.79</td>
</tr>
<tr>
<td>Galic[16]</td>
<td>2003</td>
<td>0.91</td>
<td>0.32</td>
<td>0.47</td>
<td>0.85</td>
</tr>
<tr>
<td>Hofer[17]</td>
<td>2000</td>
<td>0.92</td>
<td>0.29</td>
<td>0.46</td>
<td>0.85</td>
</tr>
<tr>
<td>Meigs[18]</td>
<td>1996</td>
<td>0.61</td>
<td>0.74</td>
<td>0.34</td>
<td>0.89</td>
</tr>
<tr>
<td>Rashid[19]</td>
<td>2012</td>
<td>0.72</td>
<td>0.46</td>
<td>0.28</td>
<td>0.85</td>
</tr>
<tr>
<td>Richie[20]</td>
<td>1993</td>
<td>0.82</td>
<td>0.48</td>
<td>0.31</td>
<td>0.90</td>
</tr>
<tr>
<td>Seo[21]</td>
<td>2007</td>
<td>0.98</td>
<td>0.04</td>
<td>0.33</td>
<td>0.87</td>
</tr>
<tr>
<td>Shahab[22]</td>
<td>2013</td>
<td>0.98</td>
<td>0.19</td>
<td>0.13</td>
<td>0.98</td>
</tr>
<tr>
<td>Tauro[23]</td>
<td>2009</td>
<td>1.00</td>
<td>0.38</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>Wymenga[24]</td>
<td>2000</td>
<td>0.95</td>
<td>0.16</td>
<td>0.44</td>
<td>0.82</td>
</tr>
<tr>
<td>This study</td>
<td>2022</td>
<td>0.95</td>
<td>0.91</td>
<td>0.11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen; PPV: positive predictive value; NPV: negative predictive value

**PSA cutoff in each age group**

Figure 2 shows the ROC curves for identifying the optimal cutoff for PSA for predicting prostate cancer in each age group. The Area Under the Curve (AUC) for patients aged 50–59 years, 60–69 years, 70–79 years, and over 80 years were 0.987 (95% confidence interval [CI], 0.982–0.992), 0.967 (95% CI, 0.955–0.979), 0.965 (95% CI, 0.961–0.974), and 0.954 (95% CI, 0.934–0.974), respectively. We also identified the optimal PSA cutoffs for the JUA age groups. The AUC for patients aged 50–64 years, 65–69 years, and over 70 years were 0.968 (95% CI, 0.939–0.996), 0.971(95% CI, 0.963–0.979), and 0.96 (95% CI, 0.954–0.965), respectively. The optimal PSA cutoffs in patients aged 50–59 years, 60–69 years, 70–79 years, over 80 years, 50–64 years, 65–69 years, and over 70 years were 3.900 ng/mL, 4.014 ng/mL, 4.080 ng/mL, 4.780 ng/mL, 3.900 ng/mL, 4.014 ng/mL, and 4.160 ng/mL, respectively. Among patients older than 80 years, the PSA threshold was higher than the conventional threshold (4.0 ng/mL). Table 3 shows the sensitivity and specificity of the city and JUA cutoffs as well as the cutoff used in this study for each age group. Compared with the conventional cutoff, the threshold in this study increased specificity from
86.2–89.9% in patients older than 80 years of age, and the false-positive rate decreased from 13.8–10.1%. Furthermore, the requirement for secondary screening decreased by 3.6%.

Table 3
Sensitivity and specificity of the city and JUA cutoffs and the cutoff used in this study in each age group.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cutoff of the City</th>
<th>Cutoff of JUA</th>
<th>Cutoff of this Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-64 yr</td>
<td>95.5/95.7</td>
<td>97.0/92.0</td>
<td>97.0/95.5</td>
</tr>
<tr>
<td>65-69 yr</td>
<td>95.0/92.9</td>
<td>95.7/90.6</td>
<td>95.0/92.9</td>
</tr>
<tr>
<td>70-79 yr</td>
<td>95.2/91.0</td>
<td>95.2/91.0</td>
<td>94.7/91.3</td>
</tr>
<tr>
<td>Over 80 yr</td>
<td>93.7/86.2</td>
<td>93.7/86.2</td>
<td>90.1/89.9</td>
</tr>
</tbody>
</table>

JUA: Japanese Urological Association

Discussion

In this study, we evaluated the accuracy of prostate cancer screening in the city in a recent cohort. The screening had high sensitivity and specificity. Although the sensitivity we observed was higher than reported in previous reports, this was thought to be attributed to no further testing for those who test negative.

Bill-Axelson et al. showed in a large cohort of patients with low-risk PCa that radical prostatectomy was associated with a reduction in mortality after 12.8 years compared to watchful waiting.[26] These data would strongly support the concept of detecting and diagnosing low-risk PCAs for young men.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 21% reduction in PCa mortality after 11 years of follow-up in screened patients.[27] The authors also recently published a 16-year follow-up update including 182,160 men, which showed that mortality was significantly lower in the screened group than in the control group.[2] The Göteborg PCa screening trial, a subanalysis of the ERSPC trial, reported that PCa mortality was reduced almost by 50% over 14 years through PSA screening among patients with a median age of 56 years and screening intervals of 2 years.[28] However, an American prostate cancer screening trial (the PLCO trial) reported that PCa mortality rates did not significantly differ between screen-detected individuals and the control group after a follow up of 7 years.[29] This difference could be because the ERSPC trial had a longer follow-up than the PLCO trial. In addition, in the PLCO trial, the percentage of the population receiving prostate cancer screening was high even in the control group, which may also explain the difference. In order to conduct large-scale screening, it is necessary to consider the false positive rate due to screening.

PSA increases not only with cancer but also with age because of prostatic hypertrophy, which may be why the PSA threshold for biopsy can be set higher for older individuals. The PSA cutoff for screening in
the city is 4.0 ng/mL. At this threshold, the sensitivity and specificity were 93.7% and 86.2%. The threshold in the over 80 years group obtained by ROC curve analysis was 4.780 ng/mL, which is higher than the conventional cutoff value. Therefore, the screening threshold in men older than 80 years should be increased. For most other age groups, the PSA thresholds obtained by ROC curve analysis were approximately 4.0 ng/mL. Therefore, in individuals aged 50–79 years, the PSA threshold for early detection of PCa could remain at the conventional cutoff value.

This study suggests that a higher threshold may be more accurate for men older than 80 years, but for men 70–79 years, the optimal threshold was similar to that of the conventional PSA threshold for early cancer detection. In the JUA guidelines for prostate cancer, the PSA thresholds for biopsy indications are 3.0 ng/mL, 3.5 ng/mL, and 4.0 ng/mL for individuals aged 50–64 years, 65–69 years, and ≥ 70 years, respectively. The fact that the PSA threshold of the city is 4.0 ng/mL, which is higher than the guideline, may be related to this result. It is thought that the juvenile threshold of JUA emphasizes reducing cancer oversight, and city threshold is adopted for optimal detection as in this study. Among individuals aged 50–64 years, our threshold yielded a false-positive rate of 4.5%, whereas the JUA guideline threshold yielded a false-positive rate of 7.9%. Both thresholds had a false-negative rate of 3.0%; therefore, the need for secondary screening was reduced by 3.9% using our threshold. Among patients aged 65–69 years, the false-positive rate decreased from 9.3% using the JUA threshold to 4.2% using our threshold; the false-negative rate increased from 4.2–5.0%, and the need for secondary screening was reduced by 3.2%. This result suggests that a higher PSA threshold may be used for men over the age of 80, which would reduce excess biopsies and cost. In the elderly, the current method of using a PSA value of 4.0 ng/mL as a cutoff, regardless of age, may not be preferable.

The present study had several limitations. First, this study did not assess mortality. Second, cancer detection rates might be underestimated, because not all participants that required secondary screening underwent prostate biopsy. Third, risk classification of the detected cancer was not evaluated. Fourthly, this study merely used a follow-up method utilizing cancer registries. Continued follow-up and evaluation of outcomes, including mortality, are needed.

**Declarations**

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**Competing Interests:** The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions:** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HT, HN, TK, SN, and KW. The first draft of the manuscript was written by HT and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
Data availability: The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics approval: The protocol for this research project has been approved by Institutional Review Board of Kanagawa Cancer Center. and it conforms to the provisions of the Declaration of Helsinki. Committee of Kanagawa Cancer Center, (Epidemiology-78).

Consent to participate: All informed consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figure 1 and 2.

Acknowledgments: We thank all patients who provided data, and all trial investigators for their contribution to data acquisition.

References


Figures
Figure 1

Sensitivity and specificity of the conventional PSA threshold (4.0 ng/mL) in each group. PSA: prostate-specific antigen
Figure 2

Receiver operating characteristic curve analysis to determine the optimal PSA cutoff for predicting prostate cancer in each group. A. 50–59 years group: The AUC is 0.987 (95% CI, 0.982–0.992) at the optimal PSA threshold of 3.900 ng/mL. B. 60–69 years group: The AUC is 0.967 (95% CI, 0.955–0.979) at the optimal PSA threshold of 4.014 ng/mL. C. 70–79 years group: The AUC is 0.965 (95% CI, 0.961–0.974) at the optimal PSA threshold of 4.080 ng/mL. D. over 80 years group: The AUC is 0.954 (95% CI,
0.934–0.974) at the optimal PSA threshold of 4.780 ng/mL. E. 50–64 years group: The AUC is 0.968 (95% CI, 0.939–0.996) at the optimal PSA threshold of 3.900 ng/mL. F. 65–69 years group: The AUC is 0.971 (95% CI, 0.963–0.979) at the optimal PSA threshold of 4.014 ng/mL. G. over 70 years group: The AUC is 0.96 (95% CI, 0.954–0.965) at the optimal PSA threshold of 4.160 ng/mL.

PSA: prostate-specific antigen; AUC: area under the curve; CI: confidence interval