Editorial

Detection Characteristics in Randomized Prostate Screening

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A recent report in Clinical Cancer Research (1) addresses detection characteristics (positive predictive value, cancer detection rates, and tumor characteristics) in men who have undergone first- and second-round screening in the Finnish randomized prostate cancer screening trial. The article (1) also reports on detection characteristics in the second round according to prostate-specific antigen (PSA) values in the first round. The authors find that a PSA value of >4.0 ng/mL and a “negative biopsy in the first screening round was associated with an up to 9-fold risk of cancer in re-screening relative to those with lower PSA levels at baseline”. The Finnish randomized screening trial is part of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Results of other centers of this study including the Dutch center are referred to in the Discussion section. This comment addresses the puzzling differences seen between the Finnish and the Dutch parts of the ESRPC with respect to the reported risk of finding cancer at re-screening according to elevated PSA values and men already biopsied in the first round. The key question is as follows: How predictive is a negative biopsy for finding cancer with another biopsy 4 years later?

Table 3 of the article (1) allows calculation of cancer detection rates of 1.3, 7.3, 11.2, and 7.6 for PSA ranges <3, 3 to 3.9, 4 to 9.9, and ≥10 ng/mL, respectively, with an average of 7.2%. Whereas these rates are not dissimilar to those seen in the Dutch protocol (Table 1), the risk ratio that uses those cancers detected with a first screen PSA < 3 ng/mL as a reference value amount to 5.6, 8.6, and 5.9 in the Finnish study (average, 5.5) and 2.7, 3.5, and 0 (average, 3.0) in the Dutch protocol.

In comparing Table 1 of this letter with Table 3 of the Finnish article (1), one major difference becomes visible: predictive value and cancer detection in those cases who had a PSA of <3 ng/mL in the first round are about two times as high in the Dutch protocol. This obviously leads to a marked difference in the denominator, explaining the differences in risk ratios.

What is the explanation?

In the Finnish protocol, rectal examination was used to determine biopsy indications in men presenting with PSA values of 3 to 3.9 ng/mL. This results in a test positive rate of only 14.7% (2) in this PSA range, whereas in the Dutch center, all these men are recommended to undergo a prostatic biopsy. The majority of men who presented with PSA values of <3.0 ng/mL at baseline screening and who have increased PSA values in round 2 progress to the PSA range 3 to 3.9 ng/mL (60.6% in the Dutch protocol). The large differences in positive predictive value (12.2 versus 25.8) and cancer detection rates (1.3 versus 2.6) in this PSA range result from the differences in biopsy indication between Finland and the Netherlands (3). By then, using the cancer detection rate as standard in calculating risk ratios, it is obvious that these will be higher in the Finnish part of the ERSPC.

What then is the truth? How predictive is a negative biopsy at baseline for prostate cancer in round 2? Next to the considerations given above, it is incorrect to assume as is done in the conclusions of the Mäkinen report that numbers of men in the baseline PSA ranges ≥ 3 are identical to those who had a “negative biopsy”. Table 1 of the report allows calculation of a biopsy rate of 22.6% of men with a PSA of 3.0 to 3.9 ng/mL and 94.0% in men with a PSA of ≥4.0 ng/mL. Unfortunately, such data for round 1 are not given. In the Dutch data, 53 of the 197 cancers (26.9%) are found in men with initial PSA ≥ 3.0 ng/mL. Five of these 53 cancers (9.5%), however, were found in men who were not biopsied at initial screening despite the PSA level of 3.0 ng/mL or more. This is due to refusals or medical reasons. Similar problems are likely to be present in the Finnish protocol.

A recent study1 applying multivariate analysis to possible predictors of prostate cancer in second-round screening actually shows negative predictive value for a negative biopsy in round 1. In addition, it must be pointed out that in second-round screening, the majority prostate cancers are found in men in low PSA ranges and in men who were not biopsied in the first round. (90.8%, 61.6%, and 36.4% for the PSA ranges 3 to 3.9, 4 to 9.9, and ≥10.0 ng/mL in second-round screening).

Another puzzling feature is the low detection rate of 2.9% in Finland versus 5.1% in the Netherlands in the first round and 2.2% versus 4.3% in the second round. These differences are probably due to differences in age distribution (55–67 years in Finland, 55–74 years in the Netherlands), the different screening regimen in the PSA range 3 to 4, and differences in the reporting of positive findings by pathology laboratories (4).

Details discussed here are of potential relevance for the future design of screening strategies, should the value of screening in terms of prostate cancer mortality be proven. The low rate of PSA progression of 10.6% to values above 3 ng/mL of those men who presented with values below 3.0 ng/mL in the first

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1 M. J. Roobol, R. Kranse, R. Raaijmakers, S. H. De Vries, and F. H. Schröder. Predictors for biopsy outcome at repeat screening: is it necessary to biopsy all men with PSA ≥ 3.0 ng/mL, submitted for publication.
round (78.5% of the total re-screened population) will be useful in the future to further prolong interscreening intervals and in determining re-screening strategies.

REFERENCES

Table 1  Dutch data of 6,239 men screened at initial and repeat screening (4-year interval) with PSA ≥ 3.0 ng/mL as biopsy indication

<table>
<thead>
<tr>
<th>PSA in first screen (ng/mL)</th>
<th>No. of men in 2nd screen</th>
<th>No. of men with PSA ≥ 3.0 ng/mL and biopsied (%)</th>
<th>No. of cancers detected</th>
<th>PPV</th>
<th>Cancer detection rate</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.9</td>
<td>2,527</td>
<td>21 (0.83)</td>
<td>4</td>
<td>19.0</td>
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<tr>
<td>1.0–1.9</td>
<td>2,189</td>
<td>177 (8.1)</td>
<td>40</td>
<td>22.6</td>
<td>1.8</td>
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<tr>
<td>2.0–2.9</td>
<td>858</td>
<td>361 (42.1)</td>
<td>100</td>
<td>27.7</td>
<td>11.6</td>
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<tr>
<td>&lt;3.0</td>
<td>5,574</td>
<td>559 (10.0)</td>
<td>144</td>
<td>25.8</td>
<td>2.6</td>
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<td>3.0–3.9</td>
<td>280</td>
<td>192 (68.6)</td>
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<tr>
<td>4.0–9.9</td>
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<td>271 (74.7)</td>
<td>33</td>
<td>12.2</td>
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<tr>
<td>1.0</td>
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<td>18 (81.8)</td>
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</tbody>
</table>

Abbreviations: PPV, positive predictive value; RR, relative risk.