The impact of reducing the prostate-specific antigen threshold and including isoform reflex tests on the performance characteristics of a prostate-cancer detection programme

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OBJECTIVE

To assess the effects on the performance characteristics, in a prostate-cancer detection programme using prostate-specific antigen (PSA) levels, of a lower PSA threshold and the incorporation of reflex (free or complexed PSA) tests.

RESULTS

Lowering the PSA threshold for biopsy referral to 2 ng/mL would increase the number of referrals from 110 to 230 per 1000 men tested, with most of the extra biopsies being among men with no cancer, i.e. an increase from 74 to 172 per 1000 men tested. However, this increased testing would result in an increase in the cancer-detection rate from 3.6% to 5.8%. Including a reflex test for men with moderately elevated PSA levels has little effect on programme performance, with only a modest (10–15%) reduction in unnecessary biopsies and a small increase in the numbers of missed cancers.

CONCLUSIONS

Lowering PSA thresholds, with or without the concurrent introduction of reflex tests, would increase both the numbers of cancers detected and the number of patients referred for biopsy procedures, of which most would be unnecessary. As the extra cancers detected are likely to be clinically localized, and with no evidence that their treatment improves the outcome of the disease, such changes place a possibly unjustified additional burden on the healthcare provider.

KEYWORDS

prostate specific antigen, free PSA, complexed PSA, reflex test, sensitivity, specificity

INTRODUCTION

The most widely used indicator to detect prostate cancer in the general population is a serum measurement of PSA; levels of >4 ng/mL are regarded as requiring further investigation, normally in the form of a prostate biopsy. Recent work suggested that there is a significant proportion of cancers occurring below this level [1], although debate remains as to their clinical significance [2]. Furthermore, when the PSA level is 4–10 ng/mL the specificity of the test is poor and a large proportion of men with no cancer are required to have a biopsy to provide a negative diagnosis (these biopsies often being referred to as "unnecessary").

Reducing the PSA threshold from 4 to 2 ng/mL would increase the overall rate of cancer detection, but it also increases the potential for over-detection, and consequently overtreatment, of clinically insignificant disease. Furthermore, lowering the test threshold will lead to a major increase in the number of men testing positively and being referred for biopsy, many of which will be unnecessary. It has been suggested that when the PSA level is <10 ng/mL, test performance can be improved, with a consequential reduction in the numbers of biopsies, by using isoform measurements, e.g. free or complexed PSA as secondary (reflex) tests.

The aim of the current study was first to quantify the effect of changing from a threshold of 4 to 2 ng/mL, and second, to address the issue of introducing a reflex testing procedure for men with moderately elevated PSA levels (either 2–10 ng/mL or 4–10 ng/mL). In both cases we quantified the effect in terms of performance characteristics of the test programme, specifically addressing the balance between sensitivity and specificity.

METHODS

For the purposes of the present study we focused on men aged <70 years, using PSA testing survey data from the UK population. This allowed us to evaluate the effect that such changes would have on a primary care-based prostate cancer detection programme in an asymptomatic population. The estimated test positive rate using a PSA threshold of 4 ng/mL for men aged <70 years is 11% [3]. The proportion of tests in primary care in England that were positive using a threshold of 2 ng/mL was 23%, and it was
estimates that 2.5% of people would have a test value of 10 ng/mL or higher [4]. Reported levels of PSA test sensitivity vary wildly, depending upon both the population being studied and the concurrent use of additional diagnostic tools, e.g. a DRE, and are the subject of considerable verification bias [5]. Recent studies provided more reliable estimates of test sensitivity by taking biopsies in all men who initially tested negatively; the Prostate Cancer Prevention Trial (PCPT) showed that even in those men with a low (<4.0 ng/mL) PSA level, a significant proportion (15%) had prostate cancer [1]. The PCPT showed clearly that only very low serum PSA levels (<0.5 ng/mL) can be considered a ‘safe’ threshold for the absence of prostate cancer on biopsy [6]. For the purposes of the present study we focused on estimates of positive predictive values (PPVs) for a range of PSA levels (Table 1). The estimates are based on the results from two sections (Rotterdam and Finland) of the European Randomised Study of Screening for Prostate Cancer (ERSPC [2,7]), as the age-distribution in these studies (range 55–70 years) is similar to that considered in the present study. These two sections used slightly different screening algorithms (see [8] for more details), although this should not affect the estimates.

A recent systematic review [9] provided detailed estimates of the sensitivity and specificity for the free to total PSA ratio test, and the complexed-PSA test as a second (reflex) test in men who have moderately elevated total PSA levels of 2–10 ng/mL. This review found that the sensitivity and specificity of free to total PSA and complexed PSA tests were comparable, and that their performance was better at PSA levels of 4–10 ng/mL than at 2–4 ng/mL, such that a reflex test could help to improve the test specificity whilst maintaining a high cancer-detection rate. Maintaining a sensitivity of 95% for the reflex test corresponds to an estimated reflex test specificity of 6% at 2–4 ng/mL, increasing to 18% at 4–10 ng/mL PSA [9].

**RESULTS**

If we assume that 1000 asymptomatic men aged 50–70 years have a PSA test, the numbers of men and cancers occurring in various PSA ranges can be calculated (Table 1). For every 1000 men who have a PSA test, 110 will be referred for a biopsy if the threshold is 4 ng/mL, whereas 230 would be referred if the threshold were lowered to 2 ng/mL, an increase of 109%. Of every 1000 men, 74 with no cancer would have a biopsy with a PSA threshold of 4 ng/mL, increasing by 132% to 172 if the threshold was reduced to 2 ng/mL (Table 2). A threshold of 4 ng/mL would correspond to a test sensitivity of 43%, specificity of 92% and cancer-detection rate of 3.6%, whilst a threshold of 2 ng/mL corresponds to a test sensitivity of 69%, a specificity of 81% and a cancer-detection rate of 5.8%.

The effect of incorporating a reflex test into the programme using a threshold of either 2 or 4 ng/mL is shown in Table 2. The use of a reflex test would reduce the numbers of biopsies by 12, to 98 per 1000 men tested if the threshold were 4 ng/mL, and by 19, to 211 per 1000 men tested if the threshold were 2 ng/mL. Table 3 and Fig. 1 show that including a reflex test reduces the number of biopsies in men with no cancer by 10–15%, but the cost is a 2% increase in the number of missed cancers in the current scenario (equivalent to one extra missed cancer per 1000 men tested) and a 8% increase with the lower PSA threshold (equivalent to an extra two missed cancers per 1000 men tested). The effect of including a reflex test on estimates of overall programme sensitivity or specificity is small; sensitivity decreases and specificity increases by ≈2%.
DISCUSSION

In this study, we considered the effect of lowering the threshold for recommending further investigation in a prostate cancer detection programme. If a threshold of 2 ng/mL rather than 4 ng/mL were adopted, this would result in a 109% increase in men being referred for further investigation, an increase in the cancer detection rate from 3.6% to 5.8%, but it would consequently result in a 132% increase in the numbers of unnecessary biopsies in men with no cancer. Including a reflex test for men with moderately elevated PSA levels would have little overall effect, with only a modest reduction in the number of these unnecessary biopsies.

The main calculations for this paper were based on results of PSA tests in the UK population. Here opportunistic prostate cancer case-finding remains low, with an estimated annual PSA testing rate of 6% in 2002, up from 3.5% in 1999 [10]. However our estimates of lowering the threshold from 4 to 2 ng/mL on sensitivity and specificity of the test are similar to those reported by the PCPT trial in the USA [6]. Unlike the PCPT trial, we were able to simultaneously assess the effect of reducing the PSA threshold and introducing a reflex test. A limitation of our study is that these results apply to asymptomatic men and are not directly relevant to men presenting in primary care with LUTS, i.e. almost half of all annual tests in primary care in 2002 in the UK [4]. However, that does not limit the implications of the current work in defining evidence-based case-finding algorithms for asymptomatic men.

The present calculations assumed that the threshold used for either the free to total PSA ratio test or the complexed PSA test would be chosen such that the reflex test sensitivity was 95%. As the reflex test sensitivity decreases, the numbers of missed cancers steadily increases, with a corresponding decrease in the numbers of unnecessary biopsies among cancer-free men. The high level of sensitivity chosen for the current study reflects the compromise between the increase in numbers of missed cancers and the decrease in numbers of unnecessary biopsies. Attempts to justify a lower sensitivity level to an individual who has a positive PSA test and negative reflex test, by balancing his decreased risk of having an unnecessary biopsy against his increased likelihood of a missed cancer, is challenging.

TABLE 3. Estimated rates of unnecessary biopsies, missed cancers and programme sensitivity and specificity for a population of 1000 men aged 50–70 years having a PSA test in a range of scenarios varying the conditions by which referral for further testing occurs

<table>
<thead>
<tr>
<th>Rates of PSA threshold, ng/mL, referral method*</th>
<th>4</th>
<th>4 + reflex at 4–10</th>
<th>2</th>
<th>2 + reflex at 2–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unnecessary biopsies in men with no cancer (1000 men tested)</td>
<td>74</td>
<td>63</td>
<td>172</td>
<td>155</td>
</tr>
<tr>
<td>Cancers missed (1000 men tested)</td>
<td>48</td>
<td>49</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Cancer detection rate, %</td>
<td>3.6</td>
<td>3.5</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>43</td>
<td>42</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>92</td>
<td>93</td>
<td>81</td>
<td>83</td>
</tr>
</tbody>
</table>

*Referral method is the threshold over which a man would be referred for biopsy, and whether or not a reflex test (and in what range) is included.

FIG. 1. Flowchart representing the outcome of 1000 men aged 50–70 years having a PSA test when the threshold for referral is 2 ng/mL. Numbers in parentheses indicate the changes when a reflex test is incorporated.

A limitation of this study is that the estimates of sensitivity, specificity and PPVs used in all the calculations are biopsy-validated estimates, and as such can be biased, as not all negative biopsies will be true negatives. There is also evidence that the biopsy regimen itself is related to the cancer detection rate, with more extensive regimens having higher detection rates [11]. Such differences will indirectly influence estimates of test performance characteristics used here. However, as this analysis used estimates from a single study, the effect of such biases will be minimized and will not affect the scenario comparisons presented here.

An issue which we have not addressed in the current study is whether to use both the PSA test and the isoform test in the same blood sample, or whether the isoform test should be assessed by a second blood sample drawn later. Natural variations in PSA have recently been shown to be associated with a coefficient of variation of ~20% [12] and a PSA level close to the threshold might affect the decision to biopsy [13]. With such fluctuations, added to known laboratory variability, and the tendency to normalize in many cases on repeat measurement, some advocate that one measurement might not be sufficiently precise for use in screening and diagnosis [13]. Our experience in the UK suggests that a single PSA level above the chosen threshold is sufficient to justify recommending prostate biopsy to avoid missing the diagnosis of significant cancers [14]. It would therefore be possible to incorporate such a test into a programme with no need to draw a second blood sample.

While lowering the threshold for referral increases the cancer detection rate, it also increases the number of biopsies taken disproportionately to the numbers of cancers detected. When the PSA level is 4.0–9.9 ng/mL, four biopsies are required per cancer detected, when it is 2.0–3.9 ng/mL this increases to five, but at 1.0–1.9 ng/mL this more than doubles number.
to 12, and if the PSA is 0–0.9 ng/mL it is 46
[15]. An issue which the present study has not
been able to address is the characteristics of the extra cancers which would be detected
if the threshold for referral were lowered.
Available evidence suggests that they are
more likely to be early-stage organ-confined
disease of limited clinical significance [1,2].
While there is some evidence that early
treatment for clinically localized disease
reduces prostate cancer and overall mortality
rates [16,17], it will be some time before data
from large-scale randomized clinical trials on
the effect of PSA testing on mortality rates are
available [18,19]. Therefore, the benefit for
either the patient or the healthcare provider
of detecting more early-stage organ-confined
disease is debatable.

Any decision to change the current guidelines
on PSA action thresholds needs careful
consideration, in light not only of the
information presented here, but also in terms
of the cost-effectiveness for the healthcare
provider, and the potential risks and benefits it
might have for the patient. In the absence of
evidence that treatment of screen-detected
clinically localized prostate cancer improves
the outcome of the disease, lowering PSA
thresholds, with or without concurrently
introducing reflex testing, will cause an
increased and possibly unjustified burden to
any healthcare provider. Ultimately the final
decision to have a PSA test and, if necessary, a
biopsy, lies with individual patients, after
being presented with all the relevant
information and uncertainties about potential
outcomes from their healthcare providers.

CONTRIBUTIONS

All authors were involved in the conception
and design of this study. A.W.R. and N.E.A.
reviewed the literature and extracted the data.
A.W.R. analysed the data and drafted the
manuscript. A.W.R. and F.C.H. were involved in
the interpretation of the results. All authors
critically reviewed the manuscript and
approved the final version.

CONFLICTS OF INTEREST

The authors declared that they have no
competing interests.

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Abbreviations: PPV, positive predictive value;
ERSPC, European Randomised Study of
Screening for Prostate Cancer; PCPT, Prostate
Cancer Prevention Trial.