Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/mL: systematic review and meta-analysis


CRD summary
This well-conducted review assessed the accuracy of the ratio of free to total prostate-specific antigen (PSA) and complexed PSA for detecting prostate cancer among men with total PSA levels between 2 and 10 ng/mL. The authors concluded that these tests can reduce the number of unnecessary biopsies whilst maintaining high cancer detection rates. These conclusions are questionable as the results presented suggest that these tests produce a high number of false positives.

Authors' objectives
To evaluate the accuracy of the ratio of free to total prostate-specific antigen (f/tPSA) or complexed PSA (cPSA) among men with total PSA (tPSA) levels between 2 and 10 ng/ml.

Searching
PubMed, Web of Science, the Cochrane Library and Cancerlit were searched from January 1986 to December 2004; the search terms were reported. Reference lists of relevant papers were screened and experts were contacted to identify additional studies. Data presented solely as meeting abstracts were excluded. Only studies reported in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to the study design were specified.

Specific interventions included in the review
Studies of f/tPSA or cPSA as a reflex test were eligible for inclusion. All assays had to be performed using commercially available kits, and both free and total PSA had to be assayed by the same manufacturer. In addition, blood had to be sampled prior to prostate manipulation or biopsy.

Reference standard test against which the new test was compared
Studies that used histology based on a single biopsy as the reference standard were eligible for inclusion. The indication for biopsy had to be independent of the f/tPSA or cPSA test result. Biopsies were either unspecified, transrectal ultrasound (TRUS) guided sextant biopsy, more than 6 cores or repeated biopsy.

Participants included in the review
Studies of men with tPSA levels between 2 and 10 ng/mL were eligible for inclusion. The studies had to include at least 10 men with prostate cancer who were not undergoing treatment at the time of recruitment. The age of the study participants ranged from 35 to 95 years and the mean age (where reported) ranged from 59 to 73 years. Study populations were referral patients or screening patients. Indications for biopsy included elevated PSA alone, elevated PSA and/or suspicious digital rectal examination (DRE), elevated PSA and non-suspicious DRE, elevated PSA and/or suspicious DRE and/or suspicious TRUS. tPSA reflex ranges were 2 to 4 ng/mL, 2 to 10 ng/mL and 4 to 10 ng/mL.

Outcomes assessed in the review
Studies that provided data on sensitivity and specificity were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data. An independent reviewer also extracted data for a random subset of studies. Sensitivity and specificity combinations at each f/tPSA and cPSA threshold within the tPSA range were extracted. Likelihood ratios for positive and negative test results were also calculated. These were used to calculate the post-test probability of disease, assuming a pre-test probability of 25%. Any disagreements were resolved through discussion.

Methods of synthesis
How were the studies combined?
Summary receiver operating characteristic (sROC) curves were calculated according to the methods of Moses and Littenberg.

How were differences between studies investigated?
The following items were investigated as possible sources of heterogeneity by including covariate terms in the sROC model: study population (screening or referral), year of recruitment, study location, age, collection of sera (prospective or retrospective), sample storage temperature, indication for biopsy, and type of biopsy procedure. The results were stratified according to tPSA range.

Results of the review
Sixty-one studies reporting 66 data sets were included; 64 data sets assessed the f/tPSA test and 19 data sets assessed the cPSA test. A total of 17,595 biopsies and 5,476 cancers were reported.

The f/t PSA test (10 studies in 2 to 4 ng/mL range, 7 studies in 2 to 10 ng/mL range and 47 studies in 4 to 10 ng/mL range) showed improved diagnostic performance in comparison with tPSA alone. There was significant heterogeneity (Wald statistic 16.3, \( p<0.01 \)) between the diagnostic performance of the f/tPSA test across the tPSA ranges. Performance was significantly higher (\( p<0.01 \)) in the 2 to 10 and 4 to 10 ng/mL tPSA ranges compared with the 2 to 4 ng/mL range. Based on the sROC analysis, at a sensitivity of 95%, specificity was 18% in the 4 to 10 ng/mL tPSA range and 6% in the 2 to 4 ng/mL tPSA range.

Among studies that measured both f/tPSA and cPSA, there were no significant differences between f/tPSA and cPSA for the detection of prostate cancer in the 4 to 10 ng/mL tPSA range. There were only three studies in the 2 to 4 ng/mL range, so it was not possible to compare their performance in this range.

There were only sufficient data to investigate heterogeneity within the f/tPSA test in the 4 to 10 ng/mL tPSA range. Within this range there were no significant differences in the following characteristics: study population, study location, age, collection of sera or sample storage temperature. Indication for biopsy, type of biopsy and year of recruitment were of borderline significance (\( p=0.05 \)).

Authors' conclusions
f/tPSA or cPSA can be used among men with tPSA levels between 2 and 10 ng/mL to reduce the number of unnecessary biopsies whilst maintaining a high cancer detection rate.

CRD commentary
This was a good review of the area. The review addressed a focused question that was supported by clearly defined inclusion criteria. The literature search was reasonable but was restricted to English language studies, thus the review may be subject to language bias. Some details of the review process were reported and these included appropriate steps to minimise bias. Although a formal validity assessment was not undertaken, some methodological features were used.
as inclusion criteria and some were investigated as possible sources of heterogeneity.

Appropriate study details were presented in a table of individual studies, while additional details were summarised in a second table. The results were a little complex to understand as the results for individual studies were not presented. However, it was likely that this was because the data were extracted for numerous thresholds from each individual study and summarising these data in a table would not have been practical. The figures used to present the results provide a very helpful overview of the data. The methods used to analyse the results were appropriate. The ROC plots and sROC curves also suggested that the accuracy of these tests was not particularly high, especially in terms of specificity (implying a high number of false positives). The authors’ conclusion that these tests may be useful in reducing the number of unnecessary biopsies is therefore questionable.

**Implications of the review for practice and research**

Practice: The authors stated that f/tPSA and cPSA tests can offer a reduction in the number of unnecessary biopsies among men with tPSA levels of 2 to 4 or 4 to 10 ng/mL, whilst maintaining a high cancer detection rate.

Research: The authors stated that further research on the use of cPSA in a variety of PSA reflex ranges and to verify the optimality of the estimated f/tPSA and cPSA thresholds is clearly warranted.

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