Is the era of prostate-specific antigen over?

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INTRODUCTION

Although PSA levels were initially used as a marker of treatment outcome and recurrence in men with prostate cancer, the potential of this test for screening was soon realized [1,2]. Few would have predicted that PSA would become such a widespread, although inconsistently used, screening tool, or that the threshold value of 4 ng/mL, chosen somewhat arbitrarily, would become a worldwide standard [2]. Nevertheless, the role of PSA testing in the mass screening of the general population remains controversial [3].

The reason for the overall performance characteristic of PSA level is that it reflects not only malignant disease, but also benign prostatic epithelial mass. It was suggested recently that, in an era when PSA testing is common, PSA is now a better marker of prostate volume than of prostate cancer. Therefore, there is currently a controversy over whether the 'PSA era' is over.

Although prostate cancer is particularly prevalent in western society [4], most men with prostate cancer do not die as a result of the malignancy [5]. In men in the USA, the annual incidence of prostate cancer is 174/100 000, with a mortality rate of 30/100 000, a ratio of 5.8 : 1. This profile is not dissimilar to that of breast cancer, which has an annual incidence of 134/100 000 and a mortality rate of 26/100 000, a ratio of 5 : 1 [4,5].

Data on lifestyle modifications and dietary interventions are inconsistent, and further prospective studies are needed [6,7]. Although PSA testing is simple and safe, considerable controversy remains over the performance of PSA testing in identifying prostate cancer. Data from the Prostate Cancer Prevention Trial (PCPT) show that the risk of a positive prostate biopsy and the risk of high-grade disease (Gleason score ≥7) increase with increasing PSA levels, but that there is no clear threshold of PSA concentration at <4.0 ng/mL that distinguishes men with prostate cancer from those without [8].

Furthermore, in contrast to previous estimates of prostate cancer risk in men with a PSA level of ≤4.0 ng/mL, the use of systematic biopsy in the PCPT population found a risk of 27% for men with a PSA level of 3.1–4.0 ng/mL, 24% for those with 2.1–3.0 ng/mL, and 17% for those with 1.1–2.0 ng/mL [7,8].

In a controversial analysis, histological variables from 1317 radical prostatectomy specimens were examined and categorized in 5-year periods of resection from 1983 to 2003 [9]. For the first 5-year period, serum PSA level was a significant predictor of the volume of the largest tumour, capsular penetration, lymph-node positivity, seminal vesicle invasion, likelihood of the largest tumour having a Gleason score of 4 or 5, and prostate weight. However, for the last 5-year period, PSA was only a significant predictor of the volume of the largest tumour and prostate weight. Do these findings indicate, as proposed by Stamey et al. [9] that ‘the PSA era is probably over for prostate cancer’? In another study, which examined 2312 radical prostatectomy specimens resected between 1992 and 2004 by one surgeon, the PSA level was significantly correlated with biochemical progression [10], whereas a further analysis of 2977 specimens, mostly from a screening study, showed that PSA level was more strongly correlated with the percentage of cancer and cancer volume than with prostate size [11].

Furthermore, the verification bias in PSA testing might also provide support for a lowered PSA threshold. Men with a 'negative' PSA test result are less likely than those with a 'positive' test result to undergo confirmatory testing by biopsy, leading to an increase in the sensitivity and a decrease in the specificity of the test. A recent analysis sought to correct for this bias by using mathematical modelling of data from 6691 men who had PSA screening for prostate cancer [12]. When receiver operating characteristic (ROC) curves for unadjusted and adjusted sensitivity and specificity were compared, the adjusted curves were more favourable for younger (age <60 years) and older (age ≥60 years) men. Overall, the adjusted ROC curves supported the idea of lowering the PSA threshold to 1.4 ng/mL in men aged <60 years [sensitivity 0.74; specificity 0.79] and to 2.1 ng/mL in men aged ≥60 years [sensitivity 0.68; specificity 0.70] [12]. Analyses of the PCPT data also showed that PSA has better sensitivity and specificity for high-grade prostate cancer than for any prostate cancer (area under the curve 0.782 vs 0.678), showing that PSA is a better marker of high-grade disease than of lower-grade disease, and that the optimum sensitivity/specificity balance is achieved at PSA levels of <4.0 ng/mL [13,14]. Although these data support a reduction in the PSA threshold, this suggestion has been a major source of controversy. Central to this debate is whether potential over-diagnosis and over-treatment are significant concerns [15].

Although the rates of cancer detection would also increase with a lower PSA threshold, doubt remains as to the proportion that would be sufficiently clinically significant to warrant intervention [14,15]. So-called ‘over-detection’ is therefore a key issue. Analysis of data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) suggests that, using a biopsy threshold of 3 ng/mL and screening at 4-year intervals for men aged 55–67 years, 48% of detected tumours would not have been detected during a man’s lifetime without screening (the definition of over-diagnosis used in this analysis) [15]. Is PSA still a valid marker for prostate cancer in second-round screening? Again, the ERSPC reported that the positive predictive value (PPV) of a PSA level of >3.0 ng/mL in first-round screening was 7.9%, compared with a PPV of 19.0–27.9% (26.3% overall) in second-round screening with the same threshold in men who had a PSA of 0–3.0 ng/mL in the first round [16]. Therefore, the PPV of PSA was maintained in the second round of screening. Evidence indicates that among men with a PSA level below a threshold of 4 ng/mL, those with a
A curable stage [17]. In the Rotterdam section infrequently as every 8 years and still have a PSA level of <1.0 ng/mL could be tested as infrequently as every 8 years and still have a small risk of aggressive cancer not detected at a curable stage [17]. In the Rotterdam section of the ERSPC, at the second screening after 4 years, only 2% of newly diagnosed cancers were in men who had a PSA level of <1.0 ng/mL at the first screening [16–18]. This increased to 21% of those with a first-screening value of 1.0–1.9 ng/mL and was largest (51%) among men with a PSA level of 2.0–2.9 ng/mL at the first screening. In all, 27% of tumours detected at the second screening were in men whose PSA level was ≥3.0 ng/mL at the first screening but who had a negative biopsy. These men either had cancer that was not detected or had cancer develop in the following 4 years. These data show that the risk of a subsequent prostate cancer diagnosis after an initially negative ‘screen’ with PSA is itself dependent on PSA level.

Another issue is the significance of a negative biopsy in the context of the PSA value. Among men with a PSA level of 4–10 ng/mL, the likelihood of a positive second biopsy after a negative one is 10–20%; whereas in those with a PSA level of 2–4 ng/mL, the likelihood is 13% after an initial biopsy detection rate of 24% [19,20]. However, data indicate that cancers detected after an initial false-negative biopsy tend to be of a lower pathological grade and stage than those detected at the first biopsy [21].

Despite concerns of over-detection and the limitation of PSA testing has had a significant effect on the diagnosis of prostate cancer [1–3,10,22]. There is much evidence from epidemiological and case-control studies that the use of PSA testing results in a stage shift, with diagnosis occurring at earlier pathological stages that are more amenable to curative treatment [13,15,23–26].

CONCLUSIONS

Over the past decade, PSA has been successfully used as a screening and early detection test. Despite statements suggesting a ‘passed era’, criticism over the sensitivity/specitivity profile of the PSA test, and doubts that PSA screening still has a role in the modern era, PSA remains the optimal biomarker for prostate cancer. Recent reports indicate that it is a better marker of more aggressive disease that requires early intervention. Although results of randomized studies on PSA screening and prostate cancer mortality are lacking, substantial evidence exists that PSA testing has a positive effect in increasing the proportion of prostate cancer diagnosed at earlier stages. Therefore, it is too early to state that the PSA era is over. How PSA is used must be redefined. Reducing the PSA threshold from 4.0 or 3.0 ng/mL has been advocated. It is becoming evident that we need to take a more flexible approach to threshold values, taking into account the age at which screening starts, and using different thresholds and screening intervals to ensure that ‘over-testing’ and the lag time to diagnosis are minimized. Finally, PSA velocity issues, doubling times, and longitudinal changes in the very low PSA range have to be re-evaluated and PSA interpretation redefined.

CONFLICTS OF INTERESTS

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Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; PCPT, Prostate Cancer Prevention Trial; PPV, positive predictive value; ROC, receiver operating characteristic.