The complexity of PSA interpretation in clinical practice

William P. Tormey a, b, *

a Department of Chemical Pathology, Beaumont Hospital, Dublin 9, Ireland
b Biomedical Sciences, University of Ulster, Coleraine, BT52 1SA Northern Ireland, UK

Abstract

Prostate specific antigen (PSA) is central to the diagnosis of prostate cancer. Laboratories quote cut-off reference ranges for PSA but values within these boundaries do not equate with an absence of cancer nor do levels above the range equate with its presence. Convention places the cut-off value at 4 $\mu g/L$ when calibrated to the Hybritech immunoassay technology and 3.0 or 3.1 $\mu g/L$ if the PSA methods are calibrated to the WHO IRP 96/670 standard. The prevalence of prostate cancer in screened normal men over 55 years of age with PSA values less than 4 $\mu g/L$ (Hybritech method) is 10.1% at a PSA of 0.6–1.0 $\mu g/L$. About 12.5% of these will be high grade. Two major randomised trials reported on PSA screening. The European trial (ERSPC) reported a risk reduction for prostate cancer death of 21% in the screened group but the US PLCO trial found no benefit. PSA results depend on calibration and there is a 22% difference between the older Hybritech and newer WHO standardisation. Biological variation in PSA is a geometric mean of 7.3%. External quality assessment schemes show wide variation in the performance of PSA analysis. Neither the American College of Physicians nor the UK National Health Service recommends screening except when there is increased risk through family history or ethnicity. Laboratories should detail their method calibration in each report and clinicians should be alerted to the potential misclassification of patients through PSA variation.

© 2014 Royal College of Surgeons of Edinburgh (Scottish charity number SC005317) and Royal College of Surgeons in Ireland. Published by Elsevier Ltd. All rights reserved.

The presence of prostate cancer

In Ireland, prostate cancer ranks first in invasive cancers diagnosed in men and accounts for 30.7% of all invasive cancers. The cumulative lifetime risk of diagnosis is 12.7% in males to age of 74 years and death is 1%. The Irish incidence rate is 149.4 per 100,000 per year and the death rate is 25.3 per 100,000 per year. The relative survival rates have improved from 68.8% in 1994–99 to 92.7% in 2005–09. In Northern Ireland in 2010, prostate cancer accounted for 11.7% of all cancer deaths in males giving a crude mortality rate of 27.9 per 100,000 males. The odds of dying from the disease before aged 75 were 1 in 84.4. For the years 2006–2010,
the European age standardised mortality rate for males was 23.0.2

In Scotland, prostate cancer ranks number 1 for invasive cancer in men and fourth overall.3 The age standardised, to the European Standard population, incidence and mortality rates per 100,000 person years at risk were 87.1 and 22.7 respectively.

Age standardised (to European standard populations) prostate cancer mortality rates in the UK overall, England, Wales and Northern Ireland in 2008–2010 were 23.8, 23.9, and 23.3 and 22.7 per 100,000 respectively.5

In the US, about 16.7% of men will be diagnosed with prostate cancer in their lifetimes up from 9% in pre-PSA times but only 2.9% will die from it. Approximately 90% are diagnosed through screening. Somewhere between 23% and 66% of men who are diagnosed with prostate cancer will have no symptoms. Prostate cancer is second to lung in cancer-related deaths in men in the US. Between 1999 and 2006, at diagnosis, 80% of prostate cancers were confined to the prostate and only 4% had metastasised.6 The 10-year risk of death varies from about 8% among men with well-differentiated tumours to 26% among those with poorly differentiated tumours. Thus laboratory estimations of PSA are central to the diagnosis of prostate cancer. But the PSA values are amongst the most difficult to interpret in clinical practice.

**Biological variation**

The PSA biological variation has a log-normal distribution and the geometric mean is 7.3% coefficient of variation with a 95th percentile value of 19.2% coefficient of variation using the Tandem-E PSA assay. Assuming an analytical variation of 5% coefficient of variation, the median critical difference, which indicates with 95% confidence that a difference is greater than what would be expected from the biological and analytical variation combined, is 20.5% and the 95th percentile critical difference was 45.8%.6 Another small study reported biological variations of 13.0% CV for free PSA, 5.6% for total PSA, 8.0% for percent free/total PSA.7 These factors are ignored in most of the literature on the subject and makes interpretation even less definitive.

**Normal PSA results**

Most US publications quote reference ranges of 0–4.0 μg/L. The innuendo in laboratory medicine is that analyte values within a reference range are assumed safe. In 2004, the placebo group in the Prostate Cancer Prevention Trial was used to determine the prevalence of prostate cancer using a six sample biopsy. All trial participants were 55 years or older. In men who never had a PSA >4.0 μg/L or an abnormal digital rectal examination, it was found that at a PSA level of less than 0.5 μg/L, 6.6% of men will have pathology proven prostate cancer. At a PSA of 0.6–1.0 μg/L, 10.1% will have prostate cancer, at levels of 2.1–3.0 which would be within the usually quoted ‘normal’ ranges 23.9% will have prostate cancer and up to levels of 3.1–4.0 μg/L when 26.9% will have prostate cancer. Of course at 4.0 μg/L more than 70% will be cancer-free. These figures were calculated from a study that took six samples biopsies. High grade cancers were recorded in 12.5% of cancers at a PSA level of 0.5 μg/L and in 25% of those cancers found where the PSA was 3.1–4.0 μg/L. PSA was measured at a central laboratory using the Tandem E assay until 2000 and subsequently the Beckman Coulter Access assay. No comparative data was provided regarding the assays.8 These data undermine the conventional case for age related reference ranges.

**PSA screening – randomised controlled trials**

There are two seminal PSA screening trials on prostate cancer mortality which inform much current practice. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial reported that after 11 years of follow-up, there was a relative reduction in the risk of death of 21% in the screened group in men aged 50–74 years and 29% after adjustment for noncompliance. To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be screened and 37 cancers would need to be detected. But there was no difference between the screened and non-screened control group in all-cause mortality.9

There was variation in aspects of the ERSPC protocol across countries. A PSA value of 3.0 μg/L was used as the cut-off indicator for prostate biopsy in most centres. In Finland, 4.0 μg/L was used as the cut-off but men with PSA values in the 3.0–3.9 μg/L range had a digital rectal examination until 1998 and from 1999, a calculation of the free PSA/total PSA ratio. The cut-off ratio was ≤0.16 and those positives were sent for biopsy. In Italy, 4.0 μg/L was used and those with PSA values between 2.5 and 3.9 μg/L had digital rectal examinations and transrectal ultrasonography. In Holland and Belgium, screening with transrectal ultrasound and digital examination was included in addition to PSA testing. The biopsy protocols also varied with Finland taking 10 to 12 biopsies.

The other trial was the Prostate, Lung, Colorectal and Ovarian (PLCO Trial) of cancer screening in the US with 76,698 men aged between 55 and 74 years which after 13 years of follow-up found no evidence of mortality benefit for annual PSA testing. The biopsy protocols also varied with Finland taking 10 to 12 biopsies.

A systematic review from the Cochrane database of five trials with 341,342 participants in 2013 did not find any significant decrease in prostate cancer-specific mortality in a meta-analysis of the five randomised controlled trials. There were significant treatment related harms. Men who have a radical prostatectomy had an 11% increased risk of urinary incontinence and a 37% increased risk of erectile dysfunction.10

The American Urological Association detailed bias and protocol contamination in their guidelines discussion.12 Contamination was 20–25% in the ERSPC trial, and 77% with a PSA screen after five years in the PLCO trial with a high exposure to PSA screening and DRE also at inclusion into the trial. Pre-screening may contributed to the lower-than-expected number of deaths on both arms in the trial.
Should we screen?

The NHS says No! “There is currently no screening programme for prostate cancer in the UK because it has not been proven that the benefits outweigh the risks”. 13

The American Urological Association in 2013 recommends no screening of men under 40 years; no screening of men aged 40 to 54 at average risk; shared decision making for men 55–69 years for PSA analysis with no routine screening of other age groups. No screening of men older than 70 years or in men with a life expectancy of less than 10–15 years. The screening interval should be two years or more. 12

The American College of Preventive Medicine in 2008 does not recommend routine screening. However high risk groups with a family history of two or more first degree relatives with prostate cancer before 65 years should be screened at 40 years and African Americans should also be especially considered because of their increased risk. 14

The American Cancer Society recommends that informed decision making discussion with each patient who has a life expectancy of at least 10 years beginning at age of 50 years. 15

Despite the international evidence, a 2013 Irish quality assurance meeting reported that more than 400,000 PSA tests were done in the Irish Republic last year. In my practice, more than 90% of PSA requests come from primary care. This is a staggering number in a total population of 4.6 million and clearly needs reform.

The downside

The US Preventive Services Task Force recommends against screening in 2012 and they report that for every 1000 men aged 55 to 69 screened every one to four years for a decade, 0 to 1 death from prostate cancer would be avoided, but 100 to 120 men would have a false positive PSA result which leads to a biopsy and one third of them will have bothersome symptoms from the biopsy. 110 men would be diagnosed with prostate cancer and 50 of these would have a complication from treatment with impotence in 29 men, urinary incontinence in 18, cardiovascular events in 2 men and deep vein thrombosis or pulmonary embolism in one man and death from treatment in less than 1 man. 16 For every 3000 men screened with a PSA test, one man will die due to complications from surgical treatment.

Prostate Cancer Intervention versus Observation Trial (PIVOT)

This was a trial of radical prostatectomy against observation for localised prostate cancer. 17 The outcome of the PIVOT trial is instructive. After 12 years of follow-up, radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality when compared to observation. The surgery group had erectile dysfunction in 81.1%, urinary incontinence in 17.1% and bowel dysfunction in 12.2% compared with 44.1%, 6.3% and 11.3% respectively in the observation group. This is a strong driver towards conservatism in these patients.

Policy of the American College of Physicians

The guidelines set out by the American College of Physicians (ACP) are published and available in full on line from the Annals of Internal Medicine dated 21st May 2013. 18 The ACP recommends no screening in average risk men under the age of 50 years or in men over the age of 69 or in men with a life expectancy of less than 10–15 years. Men between 50 and 69 should only be screened if they express a clear preference for screening and if the limited benefits and potential substantial harms are explained. The false positive rate for PSA screening is 80% when the PSA cut-off is between 2.5 and 4.0 µg/L. The problem is that 15% of men with PSA less than 4.0 µg/L will have prostate cancer on biopsy and as many as 15% of those will have higher grade (worse) cancer on microscopic examination. The most widely accepted PSA cut-off is 4.0 µg/L at present. But there is no PSA level below which there is no risk of prostate cancer.

The different rates of malignancy at PSA levels less than 4.0 µg/L quoted in peer reviewed journals are noted. 8,12 Some of this may be influenced by analytical factors.

PSA analytical factors

There are no qualifications or accreditation requirements for PSA analysis in any of the guidelines. A typical example is the fact sheet on PSA from National Cancer Institute at the National Institutes of Health in the U.S. where the accuracy and precision of PSA analytical performance in laboratories are ignored entirely. 19

The PLCO enrolled participants from 1993 to 2001 in ten study centres across the U.S. PSA tests were analysed using the Tandem-R PSA test until January 2004 and with the Access Hybritech PSA (Beckman Coulter) thereafter but all tests were analysed in a single laboratory. A PSA of greater than 4.0 µg/L was considered positive for prostate cancer. 20

The ERSPC was a multicentre trial across national boundaries. From 1994 to 2000, the Hybritech Tandem E assay was used and thereafter the Access assay was used calibrated to the original Hybritech assay. The cited performance data on the Hybritech free and total PSA assays on the Coulter Access Automated Chemiluminescent Immunoassay System across four laboratories reported an overall coefficient of variation (CV) of 3.9% for total PSA and the range was 1.8%–6.7%. For free PSA, the overall CV was 3.8% and the range was 2.5%–6.0%. 21

There was no account of the performances of the Beckman Coulter assays over the course of the ERSCP trial. It seems that the performance quality was taken for granted to reflect the original Beckman Coulter funded study. The consequences for patients of any increase in imprecision at borderline assay values and for the development of a positive bias on PSA assays are clear.

To reduce the differences between laboratories regarding PSA assays, the WHO established the first international standard in 1999 using 1 µg free PSA and 1 µg total PSA in the 90:10 PSA preparation (90% PSA–α1-antichymotrypsin and 10% free PSA). 22 The WHO calibration lead to a bias of 16%–25%
compared to the Hybritech assay calibration — the assay used to establish the 4 ng/ml cut-off widely used and quoted. A PSA cut-off of 3.0 or 3.1 µg/L should be used for WHO calibrated assays to reflect the same sensitivity/specificity profile as cut-off of 4 ng/L in the Hybritech calibrated assays. The molar absorption coefficient for PSA is 1.84 ± 0.04 (ml × mg⁻¹ × cm⁻¹) at 280 nm which is approximately 22% higher than the coefficient of 1.42 calculated by the Hybritech scientists.25

Clinicians managing patients were largely unaware that their patients PSA values would be about 20% lower if their service laboratory used the WHO IRP 96/670 standard.

Using the Beckman Coulter Access values as a 100% reference, total PSA values varied from 87% on the AxSYM and ADVIA Centaur to 115% on the Immulite analyser leading to different numbers of patients passing the cut-off for biopsy.26

### Potential effects of calibration on practice

A study of 2300 patients compared the results of PSA analysis on a Beckman Coulter Hybritech Access system and on a Bayer Diagnostics Centaur system. 55 (19%) of the 288 patients with a PSA greater than 2.6 µg/L on both instruments would have been candidates for a prostate biopsy based on Hybritech calibration data but not on Centaur WHO calibrated data.27

### External quality assessment schemes

The mean values of PSA analyses reported by external quality assessment schemes are convenient indicators of analytical variations which will have consequences for clinical practice. In the UKNEQAS distribution 137 dated 30th July 2013, there were 10 Laboratories using the Beckman Access Hybritech standard and a further 26 using the same instrument calibrated to the WHO standard. The former reported mean values of 5.5 and 17.0 µg/L and the latter 4.6 and 14.1 µg/L from two separate sample aliquots.

The Beckman Access WHO standard mean result of 4.6 µg/L has a standard deviation of 0.4. If values within 2 SDs are acceptable then that value could range from 3.8 to 5.4 µg/L. The 14.1 µg/L value has an SD of 1.1 which means that the value ranges from 11.9 to 16.3 µg/L.

A distribution on 4th March 2013 from the Randox global quality assessment scheme (RIQAS) reported an all methods mean of 6.792 µg/L but the individual means of the groups of manufacturers methods varied from a low of 3.77 for the DiaSorin Liaison to a maximum of 7.588 on the Roche Elecsys. Other RIQAS distributions revealed values that ranged from 5.5 to 13.6 µg/L in a distribution in January 2013 and from 6.8 to 14.6 µg/L in a May 2013 distribution. These variations are unlikely to be familiar to many clinicians.

### Practice propositions

The most practical solution in 2014 is that any patient aged between 50 and 69 years who actively requests PSA screening and is made aware of the downsides should be screened. There should be a shared decision making process with the patient. Those with high risk through family history or ethnicity should also be offered screening by the GP. Laboratories should reference their method and calibration in the data report. No single test should be taken as definitive.

Doctors should be made aware of the imprecision in PSA tests in any given laboratory probably by posting the quality assurance data on the web through a laboratory portal when the IT systems are capable. Ideally, patient follow-up should use the same accredited laboratory to minimise error. When watchful waiting is the policy in an individual patient, the hazard of switching laboratories for PSA analysis is clear.

WHO standards should be used for all PSA measurement calibrations worldwide. Each patient should be treated individually and opportunistic PSA screening is not indicated. For PSA values between 2 and 10 µg/L, the free to total PSA ratio is a better discriminant to separate those with benign from malignant disease than total PSA alone. The policies of rapid access clinics must be reviewed with regard to PSA. The good news is that survival in men with metastatic prostate cancer has improved from 13 to 16 months before 2005 to 40.7 months now because of treatment improvements.

In the Republic of Ireland, the lack of standardisation of PSA is an issue well known to the National Cancer Control Programme and there is currently a harmonisation group working on the issue. Age related PSA values are not clinically valid as their use provides false reassurance to both patients and physicians. The National Cancer Control Programme prostate cancer GP referral guidelines should be amended to remove the age related PSA reference ranges in the light of the published data.28

### REFERENCES


