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Review

The complexity of PSA interpretation in clinical practice

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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 μg/L when calibrated to the Hybritech immunoassay technology and 3.0 or 3.1 μg/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 μg/L (Hybritech method) is 10.1% at a PSA of 0.6–1.0 μg/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.

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.[1]

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,

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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.[4]

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.[5] 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 logg 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 man 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 screening compared to usual care which included opportunistic screening.[10]

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.[11]

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.