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Dr Pierre Durand



THE CONTROVERSIAL PROSTATE

Even if you don't work in the health professions, you have probably heard of someone dying of prostate cancer. That's how common it is.

And, of course, cancer is not the only morbidity associated with the gland.

In this newsletter, I will cover the clinical pathology aspects of prostate disease, in particular the screening recommendations using PSA. As you may know, PSA screening is not without controversy and controversy has, in fact, been a feature of the prostate since its discovery.

ANATOMICAL HISTORY OF A MYSTERIOUS GLAND

Prostate disease has been around since the very beginning. We know because our evolutionary cousins all develop prostate disease, suggesting our common ancestors suffered from similar morbidities.

Ancient humans wrote about prostatic symptoms: Egyptians reported cases of urinary retention in 3400 BC and catheterization for benign prostatic hypertrophy (BPH) was practised by Celsus and Galen in Rome.

There is also older evidence and prostatic calculi were identified in the skeletal remains of a man living in the late Pleistocene (>12,000 years ago). And the oldest cases of prostatic carcinoma date to a skeleton from the iron age (7th century BC).

Of course, at this time, the prostate as a distinct organ had not yet been discovered. The credit for that goes back, as it so often does, to the ancient Greeks.

Herophilus of Alexandra (325-255BC) wrote about the mysterious gland and Galen of Pergamon revisited the anatomy much later (129-217 AD). The pivotal role of Niccolò Massa's in 1536 in describing the prostate is usually referenced as the time when the prostate was truly identified for the first time, but as you can see, medical discoveries are usually much more convoluted. It is often impossible to credit the discovery of something to just one individual.

Despite the discrepancies and controversies, PSA screening remains important. PCa is the second most common cancer in men. There are more than 1.4 million new cases every year and more than 370,000 deaths. And the numbers are increasing. Screening, whatever the recommendations, are crucial and PSA (sometimes adding the % free PSA) is the clinical pathology standard. But as you can see from the Table above, the guidelines are not consistent.

The first issue is that PSA is not specific for PCa. It is elevated in infections, cysts, BPH, and anything that causes pressure on the gland such as digital examination, intercourse, cystoscopy or sports like cycling. The second issue concnerns the positive and negative predictive values of the PSA test. Consider, for example, that men with PSA values <1 ng/mL still have a 10% chance of harbouring clinical disease, and only 1 in 4 men with elevated PSA will be diagnosed with PCa.

What's more, 10% to 56% of cancers detected by PSA screening would not have led to symptoms and screening detects cases 5 to 12 years earlier. The latter means that there is an unnecessary period during which patients experience the harmful effects of treatment modalities like radiation or androgen deprivation. And the harmful effects are not insignificant.

There is an awful lot more written about the loss of quality of life years due to PCa screening and treatment and discussing these are beyond the scope of this newsletter. I refer you to the excellent review article above.

The identification of prostate specific antigen

Crediting someone with the discovery of the prostate specific antigen (PSA) is just as controversial as the discovery of the anatomy. PSA was independently discovered and given different names. In 1960, Flocks experimented with antigens in the prostate, one of which was surely PSA.

Ten years later, Hara characterized a unique protein in the semen fluid. He called it gamma-seminoprotein and it was later found to be the protein we now call PSA.

Numerous attempts to purify the protein followed until Wang, in 1979, achieved the purest form from semen and called it the 'prostate antigen'. In clinical medicine, we can thank Papsidero and Stamey (1980s) and others for using PSA as a marker of prostate disease. PSA was then investigated more closely and discovered to be a peptidase enzyme of the kallikrein family encoded by the KLK3 gene. The enzyme is made by the glandular epithelial cells (as an aside, PSA is also found in the paraurethral glands in women) and is important for breaking down seminal and cervical mucus, which allows the spermatozoa to migrate more easily.

Prostate specific antigen: A controversial biomarker

There is no question that the discovery of PSA made an enormous difference to disease management. But as we know, its use is still controversial.

The problem is that overdiagnosis is not without harm and the reported test sensitivities and specificities are so variable within and between populations that the cut-off values for further investigation are difficult to pin down, particular with regards prostatic carcinoma (PCa). Consider, for examples the different recommendations made by the organisations in Table 1.

Most of the information below comes from the article by Tidd-Johnson et al (2022) *Prostate cancer screening: Continued controversies and novel biomarker advancements* (Current Urology), which is an excellent review article if you wish to read more.

Trends and recommendations in South Africa (including the %fPSA assay)

In South Africa we tend to follow the recommendations made by the European Association of Urology and with global consensus still being murky, this seems like the most reasonable approach for our context. For a more granular discussion for testing guidelines in SA, please see Badenhorst et al (2024) Prostate Cancer Screening Guidelines: To PSA or Not to PSA? Wits Journal of Clinical Medicine.

One point of contention in South Africa and elsewhere is the use of the % free PSA (%fPSA), which is the ratio of free PSA (fPSA) to total PSA (tPSA). The %fPSA is helpful for detecting higher risk of PCA when the tPSA is mildly elevated.

However, as with everything about the prostate, the recommended cut-off is controversial.

%fPSA is most useful when the total PSA is 'borderline' (4-10ng/ml).

In this range, one can use the rule-of-thumb that > 25%fPSA is considered low risk for cancer, (usually cases of BPH); 10% – 25%fPSA is itself a borderline zone and a biopsy may be considered; and < 10%fPSA suggests a greater probability of PCa in which case a biopsy is often recommended.

Table 1: Prostate cancer screening recommendations using PSA (as at 2024).

Organization	Recommendation
US Preventative Services Task Force	55–69 yr: individual-specific screening based on potential harms and benefits ≥70 yr: screening via PSA should not be done.
American Cancer Society	Individual-specific screening based on harm and benefits with screening at: >50 yr for average risk, >45 yrs for high risk (first-degree relative with PCa diagnosis age <65 yr; patients of African descent, >40 yr for very high risk (>1 first-degree relative with PCa diagnosis at <50 yr)
American Urologic Association	<40 yr: not recommended 40–54 yr with average risk: not recommended <55 yr with high risk: individual-specific 55–69 yr: recommendation based on harms and benefits, ≥70 yr or a life expectancy <10–15 yr: screening not done
United Kingdom National Screening Committee	PCa screening is not recommended
European Association of Urology	Screening offered to those: >50 yr, >45 yr with family history of PCa or of African descent, >40 yr with BRCA2 mutations Men with life expectancy <15 yr are not screened

clientservices@togalab.co.za
011 663 6300
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