

“KNOW YOUR PSA”: NOT ALWAYS GOOD ADVICE

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Abstract

Men over the age of 50 are often advised to “know their PSA”, with the implicit assumption that screening for prostate cancer is effective in reducing morbidity and/or mortality. Likewise men who have received local therapy for prostate cancer routinely undergo repeated evaluation of their serum prostate specific antigen (PSA) in order to detect recurrence of disease. Here I suggest that there is no proof that knowledge of PSA improves the average life expectancy, either when used in screening of older men or to detect recurrence of disease. In contrast, there is substantial evidence that knowledge of a raised serum PSA causes substantial anxiety (PSAitis), that it identifies disease in many men that would never have become clinically apparent, and that investigations and treatments initiated because of a raised PSA cause substantial morbidity.

“Know your PSA” is a slogan used by prostate cancer advocates whose laudable goal is to decrease the mortality and morbidity due to prostate cancer. The statement implies benefit from PSA screening and many prostate cancer support groups, and the American Cancer Society, recommend that all men older than 50 with reasonable life expectancy, should have their serum PSA measured. A raised serum PSA would then lead to further investigation to rule out prostate cancer and to treat prostate cancer if it is found. Many would also apply the directive to those who have been treated for localised prostate cancer by prostatectomy or radiotherapy, so that recurrence can be detected early and to those men who have advanced disease. Is this good advice? Alan Coates and I share not only a long-time friendship, but are also men of a certain age who have made a conscious decision not to know their PSA. Here I will outline arguments to suggest that for many men knowledge of their PSA may be harmful rather than beneficial.

I will not examine in detail the arguments for and against PSA screening, which have been widely discussed elsewhere.¹⁻³ I know from the experience of giving talks to prostate cancer support groups that men diagnosed with prostate cancer by PSA screening, who have no evidence of disease after treatment by prostatectomy or radiotherapy, believe firmly that PSA screening has saved their lives. Indeed for some of them it undoubtedly has. However this is not proof of overall benefit and many of those so diagnosed and treated would have died of other causes without discovery of their occult prostate cancer in the pre-PSA era.^{2,4,5}

A Scandinavian randomised trial has shown an improvement in prostate cancer-specific and overall survival at 10 years for those with clinically-detected early prostate cancer treated by prostatectomy compared to a conservative approach, but the effect is small and confined to men <65 years old.⁶ Even if similar benefit applied to those with screen-detected cancer, which is unlikely, the number of prostatectomies needed to save one life at 10 years would be about 20. That is a large number of men undergoing the

substantial side-effects of local treatment, to ‘save’ one life, and ‘save’ is a relative term because curing prostate cancer does not buy immortality. While many men may function well after local treatment, comparison of reported side-effects of patients with those of urologists and radiotherapists tell somewhat different stories. Self-reporting by patients indicates that some degree of urinary leakage is prevalent after prostatectomy, of bowel dysfunction after radiotherapy, and that most men become functionally impotent within two years after either treatment – nerve-sparing or not.^{7,8} As Talcott⁹ has stated: “two things are certain: when screening produces a diagnosis of prostate cancer, the result is permanent sexual, urinary or bowel dysfunction much more often than a cancer death averted; and extending screening to younger patients or lowering the threshold for biopsy will tilt the balance ever more steeply toward harm.”

Large trials of PSA screening are underway, although they are threatened by contamination whereby men in the control arm obtain screening outside of the study. However, even if these very expensive studies can be completed, I don’t think they will provide convincing information about the value or not of PSA screening. This is because for practical limits on sample size, their primary endpoint is death due to prostate cancer – whereas what is more important is death due to any cause. Screening is not a totally benign procedure. While an ultrasound-directed needle biopsy of the prostate has a low chance of complications, if you biopsy a large number of men, and those who are diagnosed and treated have only a small gain in long-term survival, those complications can easily outweigh benefit. Black et al¹⁰ have reported no trends to improve all-cause mortality in cancer screening trials, although the power of studies to detect significant changes in all-cause mortality is limited. They defined some biases that might account for this – including slippery-linkage bias, where the cause of death is reported as unrelated to screening. However, if you stick enough needles into the prostates of elderly men, some of them will develop bleeding or infection and a consequent death a few months later from pulmonary embolism is likely to be reported as “unrelated”. Slippery-linkage indeed.

I am equally unconvinced of the value of PSA testing in men who have completed local treatment for prostate cancer. Certainly men who have undergone prostatectomy or radiotherapy show a substantial rate of relapse of prostate cancer and PSA testing can announce the failure of that prior treatment long before such men develop symptoms due to their disease. In most series the mean interval from rise in PSA to first symptom of disease (other than anxiety due to the PSA itself) is in the range of 5-10 years and in one large series median survival had not been reached at 15 years following the first detectable PSA after radical prostatectomy.¹¹ Serum PSA is measured routinely after local treatment but the problem is what to do if it is rising. There is no randomised evidence to indicate that treatment of such men improves their survival – and long-term hormonal treatment conveys substantial morbidity including loss of bone and muscle, anaemia and perhaps cognitive change. There is a reason that athletes are tempted to take androgens! It has been argued that radiotherapy given to men with detectable PSA after prostatectomy represents the only chance of cure. While that may be true, retrospective studies have shown that those most likely to benefit had a low Gleason score and a long PSA doubling time – properties which also identify those who may never develop symptoms due to disease.¹²

Then there are the asymptomatic men whose prostate cancer was treated conservatively, with observation or hormones, as well as those with metastatic disease that was either silent or became so after androgen ablation therapy. If these men are well and without symptoms, are they really helped by knowing that their PSA is rising? While a British Medical Research Council trial that compared early with later hormonal therapy did suggest a benefit from earlier therapy for those without evident metastases,¹³ the trial had substantial flaws. I know of no reliable evidence that early treatment will improve their longevity, as opposed to waiting until symptoms start to occur, and certainly you cannot improve the quality of life of an asymptomatic man by treating him. You can however, make it worse by telling him that his PSA is rising – PSA-dynia or PSA-itis - anxiety about PSA, is a major problem for patients who are otherwise without symptoms due to their disease.^{14,15}

There are occasions when knowledge of serum PSA might be a useful guide to therapy, such as for those with symptomatic metastatic disease who are receiving chemotherapy or other treatment – although even here improvement in pain or other symptoms may be an equal and more relevant guide to continuing or stopping therapy.¹⁶ For those involved in developing new treatments, including biological agents, PSA response or PSA progression are useful endpoints in clinical trials, but they are probably helping the investigator more than the individual patient.

The first studies of the relationship between presence of prostate cancer and the serum level of PSA appeared in 1986 and a large study in the *New England Journal of Medicine* from 1987¹⁷ established the end of peaceful coexistence between occult deposits of prostate cancer

cells and their asymptomatic hosts. Entering the terms PSA and prostate cancer into Medline now identifies more than 8000 papers. No longer do men arrive for their annual check-up in blissful ignorance that they harbour asymptomatic prostate cancer. Instead they arrive flustered and anxious, sometimes with graphs or computer print-outs – consumed by knowledge of their PSA. For many men PSA-itis is the only symptom that is caused by their prostate cancer. Others who have been screened and treated, or who are given hormonal therapy or radiotherapy after “biochemical recurrence” following radical prostatectomy, have symptoms from treatment that was given as a direct result of measurement of their serum PSA. Asymptomatic prostate cancer used to be a very common (non)-disease. Now it has become rare – replaced by a huge increase in symptomatic prostate cancer. A large number of men who 20 years ago would have had asymptomatic prostate cancer now have impaired quality of life because they are consumed by anxiety about their PSA. Such is progress. □

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