Published in final edited form as:

Nat Clin Pract Oncol. 2005 November ; 2(11): 538–539. doi:10.1038/ncponc0349.

Does current evidence justify prostate cancer screening?

Richard M Martin, BM BS PhD¹, George Davey Smith¹, and Jenny Donovan, PhD¹

¹Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol, BS8 2PR.

Screening for prostate cancer is worthwhile only if it detects potentially life-threatening tumours efficiently and safely among asymptomatic men, at a stage when lesions are curable, and if the balance of evidence convincingly demonstrates that the prospect of benefit outweighs the potential for harm.^{1,2} The debate over the value of prostate cancer screening is highly controversial, but is often fuelled by vigorous advocacy rather than the presence of robust evidence.¹

Annually, over 500,000 men worldwide are diagnosed with prostate cancer, accounting for 10% of all incident male cancers. Screening by serum prostate specific antigen testing is intuitively appealing because it identifies cancers that are localised to the prostate gland and are hence potentially curable. In contrast, most men diagnosed clinically already have locally advanced or metastatic cancers which are associated with a poorer prognosis. As there are no established primary prevention approaches, secondary prevention through screening is the only population-based approach to reducing the burden of the disease.¹ Here we review the evidence for prostate cancer screening with reference to UK criteria for the evaluation of a screening programme (http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm).

The natural history of prostate cancer

Although some histological evidence of prostate cancer is almost ubiquitous in old age, the risk of a man aged 50 years dying from prostate cancer is about 3%.¹ Estimates of the proportion of prostate cancers detected by screening which would not become clinically apparent in a man's lifetime (i.e. are over-diagnosed) vary from 48% to 84% depending on the assumptions used.^{3,4} These data reflect the fact that the natural history of prostate cancer ranges from highly aggressive in a minority to indolent in the majority. However, the rate of disease progression within different histological grades is highly variable, especially amongst men with the most common Gleason score of 6, and there are currently no markers of biologically aggressive prostate cancer which can be used to stratify individuals into the highest risk groups.

The screening test

Prostate specific antigen (PSA), a glycoprotein produced almost exclusively by the prostate gland, is the main screening test. Circulating PSA levels measured on stored serum were strongly associated with the future development of clinically defined prostate cancer incidence and mortality in the pre-PSA era^{5,6}, an association, therefore, that cannot be due to surveillance bias as a result of more intensive investigation of men with raised PSA.

Corresponding author: Richard Martin Tel: +44 (0) 117 928 7321, Fax: +44 (0) 117 928 7236 richard.martin@bristol.ac.uk.

Conflicts of interest: RMM and JD are principal investigators on a randomised controlled trial of the potential population impact of PSA testing for prostate cancer in the UK (Comparison arm for ProtecT trial, CAP), funded by Cancer Research UK/UK Department of Health, and the NHS Health Technology Assessment Programme.

However, while PSA levels are a strong risk factor for prostate cancer, diagnosis can be made only after a biopsy. Recent findings from the Prostate Cancer Prevention Trial indicate that there is a continuum of increased risk of prostate cancer with increasing PSA levels, even at levels well below currently recommended cut-offs,⁷ and no threshold PSA value for undertaking a diagnostic biopsy offers simultaneously high sensitivity and specificity.⁸ This Trial offered a unique opportunity to assess the sensitivity of PSA screening without verification bias because all men underwent an end-of-study prostate biopsy after seven years of follow-up, regardless of PSA levels or digital rectal examination (DRE) findings⁷ (see Box for definitions of sensitivity, specificity and verification bias). In this study, 15% of 2950 men aged between 62-91 years, with PSA levels less than 3.0 ng/ml at baseline and less than 4.0 ng/ml at all the subsequent annual follow-up visits, were diagnosed with previously undetected prostate cancer at the end-of-study biopsy.⁷ The sensitivity (specificity) of PSA testing at threshold levels of 1.1, 2.6 and 4.1 ng/ml were 83.4% (38.9%), 40.5% (81.1%) and 20.5% (93.8%).⁸

Some of the tumours detected at these low levels of PSA may be clinically important. 15% of the cancers detected after biopsy in the Prostate Cancer Prevention Trial in men with PSA values less than 4.0 ng/ml were high grade (Gleason score of 7 or more)⁷ and in the Physicians Health Study⁵ there was a gradation of increasing risk of subsequent clinically defined prostate cancer with increasing levels of PSA in the normal range. There is thus no PSA value below which a man can be assured that he does not have potentially important prostate cancer. Concerns about an appropriate cut-off point have led to biopsies now being done on all men with PSA levels of 3 ng/ml and higher in recent screening trials¹ and a threshold value of 2.6 ng/ml has recently been recommended for screening. Such reactions fail to appreciate that screening is a programme not a test and that it is essential to evaluate what happens as at all stages of the screening process.¹ The large difference between a man's risk of death from prostate cancer (about 3%) and life-time risk of having microscopic evidence of prostate cancer (42% for a man of 50 years),¹ suggests that the vast majority of prostate cancers detected by screening will be clinically unimportant. Indeed, as the intensity of the screening effort has increased in the PSA era the prostate cancers that are being identified are increasingly less likely to be palpable on DRE, and are becoming smaller, of lower grade and of lower invasiveness.⁹ The key dilemma currently is that, although most cancers detected by screening are clinically confined to the prostate,⁹ and hence potentially curable,¹⁰ current screening tests cannot differentiate between the majority of screen-detected cancers that have low biological likelihood of progression (for which radical treatments are probably being offered unnecessarily¹) from those with aggressive potential, in whom early radical treatment may or may not be justified.¹⁰

Treatments for screen-detected prostate cancer

Published studies about the effectiveness of the main treatments for localised prostate cancer (radical prostatectomy, radical radiotherapy, brachytherapy, and active monitoring) are limited by their tendency to be observational in design, small in scale and insufficiently robust. A randomised controlled trial from Scandinavia, showed that radical prostatectomy for localised prostate cancer reduced the risk of all-cause and prostate cancer specific mortality at 10 years by approximately 25% and 44%, respectively, when compared with watchful waiting.¹⁰ However, this study may have little relevance for screening as only 11% of the men had screen detected prostate cancer. The doubts surrounding the benefits of screening and early radical treatment have led to increasing use of active monitoring, involving regular PSA, clinical and sometimes histological follow-up with the aim of determining when cancers should be treated by potentially curative interventions. However, the most appropriate frequency and form of follow-up in patients choosing active monitoring remains undefined (Martin RM, submitted paper, 2005). Each of the treatments

for localised prostate cancer can have deleterious side effects,² and evidence from randomised trials about the effectiveness and side-effects of treatment for screen-detected disease is urgently required.

Are screening programmes effective?

It has been suggested that the decline in prostate cancer mortality during the 1990s reported in Canada, the USA, Austria, France, Germany, Italy and the UK was due to the increased use of PSA screening. However, the pattern of change in mortality is inconsistent between and within countries.¹¹ In the USA the mortality decline seems to have occurred very soon after the start of PSA testing, before the effects of any treatment of screen-detected disease could be credibly observed. In the UK and other countries there was a decline in mortality with no major increase in PSA testing.¹¹ Other factors are likely to have contributed to the secular decrease in mortality from prostate cancer, including improved treatment of clinically detected disease. In a study comparing cohorts of men from Seattle-Puget Sound (where there was rapid uptake of PSA screening and prostate cancer treatment) and Connecticut (where testing was much less common), no differences in mortality were found, even with an appropriate time lag and 11 years of follow-up.¹² The problems of attributing causality in these sorts of observational studies are well known and robust evidence can only come from randomised trials of screening programmes: these are underway in Europe (ERSPC), the USA (PLCO) and the UK (Comparison arm for ProtecT trial, CAP).

Conclusions

In any screening program some people will benefit but others will be harmed as a result of their participation. The challenge is to assess whether a screening programme does more good than harm. With PSA testing, there is potential for screening to result in considerable over-diagnosis and over-treatment of clinically insignificant prostate cancer³, with little evidence of mortality benefit¹² and the prospect of substantial treatment-related morbidity.² For every 1 million men who undergo PSA testing, about 100,000 would have a raised PSA result and face anxiety over possible cancer and the need for biopsy.¹ Approximately 20,000 men would be diagnosed with cancer, and 80,000 face the burden of an un-quantified future risk of prostate cancer. If one half of those diagnosed with localised disease (10,000) underwent radical prostatectomy, conservative estimates would suggest that 10 would die of the operation, and around 300 would develop severe urinary incontinence and 4,000 impotence. The number whose prostate cancer would eventually have impinged upon their lives is currently unknown, as is the number of deaths that would have been prevented. Ongoing randomised trials will provide robust evidence about current screening programmes. Until biological markers are identified which will predict aggressive cancers and aid the individualisation of patient management, the likelihood of harm may outweigh the prospect of benefit. We conclude that screening for prostate cancer is currently unjustified outside randomised controlled trials investigating its effects.

Box

Definitions of epidemiological terms

Sensitivity: the proportion of true positives correctly identified as such e.g. at a sensitivity of 20.5%, 79.5% of prostate cancers would be missed.

Specificity: the proportion of true negatives correctly identified as such i.e. at a specificity of 93.8%, the false positive rate would be 6.2%.

Verification bias: This arises because biopsies are generally performed only when PSA levels are raised or a digital rectal examination is clinically suspicious. If not all test

negatives undergo a biopsy, the false negative rate is underestimated and the sensitivity of the test is overestimated.

Reference List

1. Frankel S, Smith G Davey, Donovan J, Neal D. Screening for prostate cancer. *Lancet*. 2003; 361(9363):1122–8. [PubMed: 12672328]
2. Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and Sexual Function After Radical Prostatectomy for Clinically Localized Prostate Cancer: The Prostate Cancer Outcomes Study. *JAMA: The Journal Of The American Medical Association*. 2000; 283(3): 354–60. [PubMed: 10647798]
3. McGregor M, Hanley JA, Boivin JF, McLean RG. Screening for prostate cancer: estimating the magnitude of overdiagnosis. *CMAJ*. 1998; 159(11):1368–72. [PubMed: 9861205]
4. Draisma G, Boer R, Otto SJ, van der Cruysen IW, Damhuis RAM, Schroder FH, et al. Lead Times and Overdiagnosis Due to Prostate-Specific Antigen Screening: Estimates From the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst*. 2003; 95(12):868–78. [PubMed: 12813170]
5. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA: The Journal Of The American Medical Association*. 1995; 273(4):289–94. [PubMed: 7529341]
6. Hakama M, Stenman UH, Aromaa A, Leinonen J, Hakulinen T, Knekt P. Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. *Journal of Urology*. 2001; 166(6):2189–91. [PubMed: 11696733]
7. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter. *N Engl J Med*. 2004; 350(22):2239–46. [PubMed: 15163773]
8. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ, et al. Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower. *JAMA: The Journal Of The American Medical Association*. 2005; 294(1):66–70. [PubMed: 15998892]
9. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenex M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what has happened in the last 20 years. *Journal of Urology*. 2004; 172:1297–301. [PubMed: 15371827]
10. Bill-Axelsson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. *New England Journal of Medicine*. 2005; 352(19):1977–84. [PubMed: 15888698]
11. Oliver SE, Gunnell D, Donovan JL. Comparison of trends in prostate-cancer mortality in England and Wales and the USA. *The Lancet*. 2000; 355(9217):1788–9.
12. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ*. 2002; 325(7367):740. [PubMed: 12364300]