Prostate cancer: screening approaches

Introducing screening for prostate cancer requires evidence that this would do more good than harm. Current evidence about the impact and natural history of prostate cancer, screening and diagnostic tests, and the effectiveness of treatments is reviewed below.

The principal first-line screening test for prostate cancer is the prostate-specific antigen (PSA) blood test. However, the presence of prostate cancer can only be confirmed following examination of prostate tissue removed either following ultrasound-guided or systematic (random) biopsies or transurethral resection of the prostate. PSA is raised (above 3.0 ng/ml) in approximately 10% of men aged 50–69 years, and if these men receive biopsy, around 20% will be found to have prostate cancer which is confined to the gland (localized) and thus potentially curable (Donovan et al, 2003). However, the majority of men diagnosed with localized prostate cancer will not die of it – prostate cancer is often slow-growing and other causes of death commonly intervene before it becomes clinically apparent. Screening for prostate cancer in men in the population is thus highly controversial (Frankel et al, 2003). Currently in the UK, screening is not recommended. Men over 50 years of age are advised to discuss the issues around screening with their GPs. If, having received this information, they still wish to proceed, they can ask for a PSA test within the NHS.

While screening for prostate cancer using PSA may seem intuitively appealing, there are many serious and contentious issues to consider before the testing of healthy men can be recommended. In particular, the NHS must await evidence that shows that PSA testing of men in the population would do more good than harm. The UK National Screening Committee has published a set of criteria to evaluate screening programmes, each of which needs to be satisfied to allow the introduction of screening (http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm). Each of these criteria is considered below in relation to prostate cancer.

Is prostate cancer an important health problem?

There can be no question that prostate cancer is a serious public health problem. More than 500 000 men are diagnosed with prostate cancer each year around the world, and it is rapidly becoming the most common cancer in men. In the UK, nearly 30 000 cases are diagnosed each year, and more than 10 000 die from prostate cancer each year (Toms, 2004). As men age, and PSA testing increases, the number of men with prostate cancer will continue to rise. As the UK does not conduct screening, most men currently diagnosed in the UK present with symptoms of locally advanced or metastatic cancer. These men have a poor prognosis (Rosen, 1995).

Do we understand the natural history of prostate cancer, and is there a 'latent period'?

The natural history of prostate cancer is not well understood. Autopsy and post mortem studies show that cancerous cells can be found in the prostates of 30–40% of men at the age of 60 years, rising to 60–70% by the age of 80 years, yet the eventual risk of death from prostate cancer is only about 3% for a 50-year-old man (Whitmore, 1994). These data reflect the fact that a minority of prostate tumours are highly aggressive and life-threatening, and the majority are slow-growing and indolent. The aggressiveness of prostate cancer is indicated by the pathological (Gleason) grade. The Gleason 'sum' is made by adding the score (*Figure 1*) for the most dominant pattern in the tumour with the score for the second most common pattern. A Gleason score 8 has a worse prognosis than a Gleason 6. Men diagnosed with localized prostate cancer between 1971 and 1984 in Connecticut and treated conservatively faced a 4–7% chance of dying from prostate cancer within 15 years of diagnosis with tumours with Gleason scores of 2–4, compared with 18–30% for the most common Gleason score 6, and 60–80% for those with the highest scores of 8–10 (Albertsen et al, 1998).

Screening using PSA with a cut-off point of 3.0 ng/ml detects tumours most commonly with a Gleason score of 6, and the rate of disease progression in these men is highly variable. A recent paper has shown that men diagnosed with a Gleason score of 6 faced only a modest risk of dying of prostate cancer (27%) after 20 years of follow up (Albertsen et al, 2005). There are currently no markers of biologically aggressive prostate cancer that can be used to stratify individuals into the highest risk groups. Estimates of the proportion of prostate cancers detected by PSA 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

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(McGregor et al, 1998; Draisma et al, 2003). Thus the well-known aphorism is true – that more men die with prostate cancer (without knowing it) than of it.

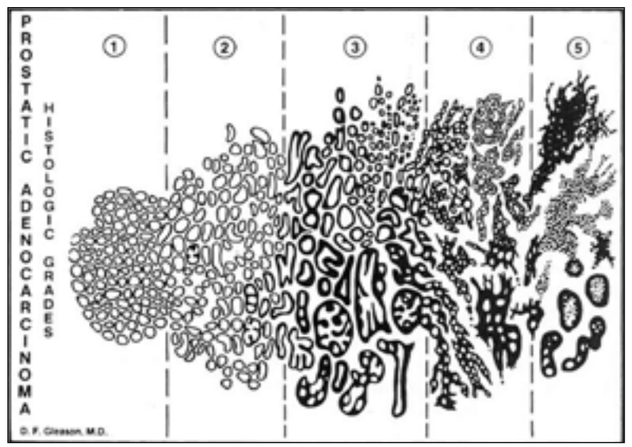
Are there primary prevention interventions?

There are currently no interventions available that could prevent the development of prostate cancer. The only clearly established risk factor for prostate cancer is increasing age (Gronberg, 2003). Having an affected first-degree relative doubles the risk of developing prostate cancer, although major susceptibility genes account for only 5–10% of prostate cancer cases (Ostrander et al, 2004). Diet has been associated with prostate cancer, but none of the findings approaches the level at which nutritional recommendations aimed at primary prevention could be made. There is great interest in chemoprevention strategies, but with the current lack of robust evidence, primary prevention remains a future aspiration.

Is there a simple, safe, acceptable, precise and validated screening test and diagnostic process?

A digital rectal examination is an essential part of a urological investigation but it has been shown to have little value as a screening test in the general population. The main initial screening test is the serum concentration of PSA, and this has to be followed by transrectal biopsy. Men are selected for biopsy if their PSA level exceeds the 'normal' level. There is, however, considerable controversy over the appropriate cut-off point to trigger referral for biopsy. For example, the NHS uses age-based ranges, so that an abnormal result is over 3.0 ng/ml in men aged 50–59 years of age and over 4.0 ng/ml in those aged 60–69 years of age, but the European trial of screening (ERSPC) and ProtecT studies use a single cut-off point of 3.0 ng/ml.

Figure 1. Gleason grade.



As indicated above, approximately 10% of men aged 50–69 years agreeing to PSA testing in the UK have a PSA over 3.0 ng/ml (Donovan et al, 2003). Most of these will agree to biopsy, but only around 20% will have a positive result indicating the presence of localized cancer (Donovan et al, 2003). Circulating serum PSA concentrations are influenced by age and prostate size as well as the presence of prostate cancer, and can also be raised after ejaculation, acute urinary retention, prostate biopsy, surgery or prostatitis. PSA is thus indicative of prostate cancer, but as it can be raised for several reasons, it leads to a large number of men being identified as 'false-positives' – having an abnormal PSA level but later negative biopsy. In terms of acceptability, the simple PSA blood test is safe and acceptable, but biopsy can be painful and can cause some morbidity, including discomfort or pain, difficulty voiding, haematuria, and, more rarely septicaemia, acute urinary retention and, very rarely, even death (Crundwell et al, 1999). Thus screening for prostate cancer is not simply a matter of taking a blood test – there is a pathway to diagnosis that may include biopsy and may not necessarily end in a clear outcome (particularly, for example, for the 7% of men tested who have a raised PSA level and negative first biopsy).

The Prostate Cancer Prevention Trial (PCPT) investigated the impact of finasteride in preventing prostate cancer (Thompson et al, 2004). Men recruited to PCPT were biopsied both at the beginning and end of the study, providing evidence about levels of prostate cancer among men with what are considered to be 'normal' levels of PSA. This study confirmed that there is a continuum of increased risk of prostate cancer with increasing PSA levels, and that this occurs even at levels well below currently recommended cut-off points of 4.0 ng/ml or 3.0 ng/ml (Thompson et al, 2004). Thus 15% of 2950 men aged between 62 and 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 (Thompson et al, 2005). Some of the tumours detected at these low levels of PSA were high grade (Gleason score of 7 or more). Thus, in addition to PSA testing producing false positives (men alerted to the risk of cancer and undergoing further testing but later reassured by negative biopsy), it also causes 'false negatives' (men reassured that their PSA level is normal and usually not further tested, who actually do have prostate cancer).

This relative lack of accuracy of PSA testing has led some to call for a reduction in the cut-off point for biopsy. Such a move might detect some of the cancers currently missed, but it would not detect all and it would markedly increase the numbers of men being biopsied unnecessarily. 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 who is 50 years of age), suggests that the majority of prostate cancers detected by screening are clinically unimportant.

The key dilemma currently is that, although most cancers detected by screening are clinically confined to the prostate and hence potentially curable, screening tests cannot differentiate between the majority of screen-detected cancers that have low biological likelihood of progression (for which radical treatments would probably be unnecessary and, for some, harmful) and those with aggressive potential, in whom early radical treatment might be beneficial.

Is there an effective treatment for screen-detected prostate cancer?

Treatments for localized prostate cancer include radical prostatectomy, radical radiotherapy, brachytherapy, hormone manipulation, or programmes of monitoring, variously termed 'watchful waiting', 'surveillance' or 'active monitoring' (Jani et al, 2003). Robust published evidence about the effectiveness of these treatments is scant; there are few randomized controlled trials, and the majority of studies are observational in design, necessitating care in interpreting their findings. All the studies of treatment of screen-detected disease indicate that men will do well whichever treatment they receive, primarily because of the small number of prostate tumours that develop to threaten length or quality of life.

None of the treatments has a proven mortality advantage for screen-detected disease and there are, as yet, no published randomized trials of treatment of screen-detected disease. The US PIVOT (Wilt et al, 1994) and UK ProtecT (Donovan et al, 2002) trials are underway but it will be several years before they report. An important randomized trial from Scandinavia has compared radical prostatectomy with watchful waiting for men with clinically localized prostate cancer determined in the pre-PSA era. This trial showed that prostatectomy 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 (Bill-Axelson et al, 2005). However, the absolute reductions in risk of all-cause and prostate cancer-specific mortality were small (around 5%), and this study has limited relevance for screening as only 11% of these men had screen-detected prostate cancer.

Each of the treatments for localized prostate cancer can have deleterious side effects, reported at various levels depending on patient selection, specialist skill and throughput (Begg et al, 2002). Radical prostatectomy, for example, can lead to 2–5% of men having severe incontinence, up to one half experiencing some leakage of urine, and between 10 and 90% experiencing erectile difficulties (Steineck et al, 2002). However, data on the particular outcomes of each of the treatments are lacking in precision and detail. Evidence from randomized trials of treatment in the PSA era are urgently required.

Is there evidence from high-quality randomized controlled trials that screening reduces mortality or morbidity?

No robust randomized trials of screening for prostate cancer have yet been published. There are such studies underway in Europe (Europe Randomized Study of Screening for Prostate Cancer), USA (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) and the potential impact of PSA testing is now being investigated in the UK through the CAP (Comparison Arm for ProtecT) study. In the absence of trial findings, some evidence is available from ecological studies and case-control/cohort studies, but these are often difficult to interpret. For example, it was suggested that the decline in prostate cancer mortality during the 1990s in several countries was a result of the increased use of PSA testing. However, the pattern of change in mortality was inconsistent between and within countries, and falls in mortality were found in countries without widespread screening (such as the UK) as well as those with it (such as the USA) (Oliver et al, 2000).

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 uncommon), no differences in mortality were found, even with 11 years of follow up (Lu-Yao et al, 2002). Other factors are likely to have contributed to the decrease in mortality from prostate cancer over time, including improved treatment of clinically detected disease. Again, evidence from well-conducted trials of screening is urgently required.

Conclusions

There is, as yet, little robust evidence that could support the introduction of screening for prostate cancer. In any screening programme, some people will benefit but others will be harmed as a result of their participation. With PSA testing, there is potential for screening to result in considerable over-diagnosis and over-treatment of clinically insignificant prostate cancer, with little evidence of mortality benefit and the prospect of substantial treatment-related morbidity. For every 100 000 men who undergo PSA testing, about 10 000 would have a raised PSA result and face anxiety over possible cancer and the need for biopsy. Approximately 2000 men would be diagnosed with cancer, and 8000 face the burden of an unquantified future risk of prostate cancer. If one half of those diagnosed with localized disease (1000) underwent radical prostatectomy, conservative estimates would suggests that one man would die of the operation, around 30 men would develop severe urinary incontinence and 40 men would experience impotence. The number whose prostate cancer would eventually have threatened their length or quality of life is unknown, as is the number of deaths that might be have been prevented. Until biological markers are identified which will predict aggressive prostate cancers and aid the individualization of patient management, the

likelihood of harm currently outweighs the prospect of benefit. The authors conclude that screening for prostate cancer is currently unjustified outside randomized controlled trials investigating its effects. **BJHM**

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Albertsen PC, Hanley JA, Fine J (2005) 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* **293:** 2095–101

Begg CB, Riedel ER, Bach PB et al (2002) Variations in morbidity after radical prostatectomy. *N Engl J Med* **346**(15): 1138–44

Bill-Axelson A, Holmberg L, Ruutu M et al (2005) Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* **352**(19): 1977–84

Crundwell MC, Cooke PW, Wallace DM (1999) Patients' tolerance of transrectal ultrasound-guided prostatic biopsy: an audit of 104 cases. *BJU Int* **83**(7): 792–5

Donovan J, Mills N, Smith M et al (2002) Quality improvement report: improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ* **325**(7367): 766–70

Donovan JL, Hamdy FC, Neal DE et al (2003) Prostate testing for cancer and Treatment (ProtecT) feasibility study. *Health Technol Assess* **7**(14): 1–42

Draisma G, Boer R, Otto SJ et al (2003) lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* **95**(12): 868–78

Frankel S, Davey Smith G, Donovan J, Neal D (2003) Screening for prostate cancer. *Lancet* **361**(9363): 1122–8

Gronberg H (2003) Prostate cancer epidemiology. *Lancet* **361**(9360): 859–64

Jani AB, Hellman S (2003) Early prostate cancer: clinical decision-making. *Lancet* **361**(9362): 1045–53

Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ (2002) Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ* **325**(7367): 740–6

McGregor M, Hanley JA, Boivin JF, McLean RG (1998) Screening for prostate cancer: estimating the magnitude of overdetection. *CMAJ* **159**(11): 1368–72

Oliver SE, Gunnell D, Donovan JL (2000) Comparison of trends in prostate-cancer mortality in England and Wales and the USA. *Lancet* **355**(9217): 1788–9

Ostrander EA, Markianos K, Stanford JL (2004) Finding prostate cancer susceptibility genes. *Annu Rev Genomics Hum Genet* **5**(1): 151–75

Rosen MA (1995) Impact of prostate-specific antigen screening on the natural history of prostate cancer. *Urology* **46**(6): 757–68

Steineck G, Helgesen F, Adolfsson J et al (2002) Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* **347:** 790–6

Thompson IM, Pauler DK, Goodman PJ et al (2004) Prevalence of prostate cancer among men with a prostate-specific antigen level <=4.0 ng per milliliter. *N Engl J Med* **350**(22): 2239–46

Thompson IM, Ankerst DP, Chi C et al (2005) Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/mL or lower. *JAMA*: **294**(1): 66–70

Toms JR, ed. (2004) *CancerStats Monograph*. Cancer Research UK, London

Whitmore WF Jr (1994) Localised prostatic cancer: management and detection issues. *Lancet* **343**(8908): 1263–7

Wilt TJ, Brawer MK (1994) The prostate cancer intervention versus observation trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *J Urol* **152:** 1910–14

KEY POINTS

- There is currently insufficient evidence to recommend population screening for prostate cancer.
- Further research is required to to understand the natural history of prostate cancer to improve screening tests and to evaluate treatment strategies.
- While current screening tests can identify potentially curable prostate cancers, it is not possible to distinguish aggressive from latent prostate cancers and thus there is clear potential for screening to lead to unnecessary treatment.
- Screening for prostate cancer is unjustified outside randomized trials to evaluate impact.