Screening for prostate cancer: the current position

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Prostate cancer is a significant and increasing health problem in the UK and elsewhere, and there is considerable interest in the potential for screening. Of the currently available screening tests, measurement of serum levels of prostate specific antigen appears the most promising. However, despite evidence that screening can detect asymptomatic early stage disease, there is, as yet, no evidence that mortality from prostate cancer can be reduced.

There are concerns that screening may result in considerable over-diagnosis of non-progressive or slowly developing disease, and the effectiveness of radical treatment of localised disease, which itself will cause some morbidity, remains a subject of debate. Population screening should not currently be recommended. Randomised controlled trials are in progress to assess the effectiveness of screening, but these will take many years to produce results.

Screening for prostate cancer has been a controversial subject for a number of years. Prostate cancer is of increasing public health importance in view of the ageing of the population and increasing mortality from this cancer. These changes have been accompanied by an increased demand for the earlier detection of prostate cancer through screening on the assumption that earlier treatment reduces mortality. However, the effectiveness of population screening in reducing mortality from prostate cancer remains unproven and must await the outcome of randomised controlled trials currently in progress or planned both in Europe and the US. In the meantime, it is the potential for harm that has led some to question whether even a randomised trial is ethical. The difficulty arises from the recognition that many more men will die with prostate cancer, often undiagnosed as shown by autopsy studies, than will die of the disease, suggesting that the natural history may encompass latent or very slow-growing disease. This is compounded both by the uncertainty surrounding the effectiveness of radical treatment compared with surveillance, and by the morbidity which may be caused by this treatment. In this chapter we address the current knowledge on these issues, and review what are, and should be, the present recommendations on screening for prostate cancer.
The extent of the problem

Mortality rates for prostate cancer have been rising in many countries with white populations during the past few decades\(^2\). Prostate cancer is now one of the most frequent causes of cancer death in men in the US, with about 41,000 deaths per year\(^3\). In England and Wales, prostate cancer is the second commonest cause of death after cancer of the lung: in 1994, there were 8,689 deaths from prostate cancer, a mortality rate of 34.0 per 10^5 (30.3 per 10^5 adjusted to the European standard population)\(^4\). The mortality rate rises steeply with age, with 93% of deaths occurring in men aged over 64 years. During 1971 to 1994, the mortality rate increased in all age groups (Fig. 1).

Prostate cancer is one of the most frequently diagnosed cancers in men both in the US and in England and Wales. There are estimated to be 209,900 American men diagnosed each year\(^5\). In England and Wales in 1991, there were 13,940 new cases registered, an incidence rate of 55.8 per 10^5 (48.9 per 10^5 adjusted to the European standard population)\(^6\). Incidence rises steeply with age although less so than mortality. In England and Wales, 88% of new cases occur in men aged over 64 years. From 1971 to 1991, the incidence rate has increased in all age groups (Fig. 2). Incidence rates have also been rising world-wide during the past few decades\(^2\). In part, this rise may reflect improved ascertainment...
through cancer registries, increased diagnosis due to the use of transurethral prostatectomy and, more recently, screening with prostate specific antigen tests. It is possible, however, that there has also been a true rise in incidence. The 5 year survival rate in men with prostate cancer relative to the general population has been increasing in countries such as US, and England and Wales\(^7\). As there has been little change in the survival of men with metastatic disease\(^8\), this supports the suggestion that there has been increasing diagnosis of early stage disease. There are no reliable routinely collected data on stage-specific incidence to confirm this.

**Screening tests for prostate cancer**

Of the three commonly proposed screening tests for prostate cancer – digital rectal examination, transrectal ultrasound, and measurement of serum levels of prostate specific antigen (PSA) – the last of these is currently the most promising, although new markers continue to be identified.

**Digital rectal examination**

Digital rectal examination has been in use for case finding, or as a screening test for a number of years. The reported sensitivity and specificity
are lower than that of PSA\(^9\) and the test may be of limited value in detecting early stage disease\(^10\). Thus, although its use in combination with PSA may increase the yield and sensitivity of screening slightly, it is likely also to decrease specificity and may be less acceptable as a screening test. Its accuracy is also dependent on the interpretation of the examiner\(^11\). The use of digital rectal examination can be likened to the addition of clinical examination to mammography; as with the latter, improvements in the accuracy and referral criteria for PSA testing are likely to render the marginal benefit of including digital rectal examination smaller in the future.

**Transrectal ultrasound**

Transrectal ultrasound has the disadvantage of being a time-consuming and invasive procedure, and is largely now regarded as a secondary diagnostic test rather than an initial screening test; its main use is in the performance of ultrasound guided biopsies.

**Prostate specific antigen serum levels**

Since the recognition that total PSA values are increased in men with prostate cancer compared with levels in healthy men, considerable work has gone into improving the validity of the test. The aims are firstly to increase the sensitivity and specificity of the test to detect men with cancer, and secondly to distinguish those cancers more likely to progress and to cause morbidity and/or mortality in the lifetime of the man screened. The latter aim is as important as the first in order to avoid considerable over-diagnosis and over-treatment.

Early studies of series of men screened by PSA testing have generally identified a level of total PSA greater than 4 ng/ml as the criteria for further investigation, *i.e.* as the definition of a ‘positive screening test’. Further work has concentrated on increasing the specificity, by the identification of additional criteria, particularly for levels in the 4–10 ng/ml range, and improving sensitivity, by identifying additional criteria to be applied when the total PSA is less than 4 ng/ml. The use of age-specific reference levels has been proposed, based on evidence that PSA levels in healthy men increase with age\(^12\). Other suggested measures include PSA velocity (the rate of change of PSA levels over time)\(^13\), and age-specific PSA velocity\(^14\). PSA density (serum PSA divided by prostate volume) has also been proposed as a means of distinguishing between prostate cancer and benign prostatic hypertrophy\(^15\).

However, comparisons of PSA levels between studies and over time are potentially hampered by inter-laboratory variation between assays used,
with different assays involving different reference levels. In addition, it is now recognised that, in healthy men, the level of PSA may vary in serial samples, with coefficients of variation of 16–24%, rendering the use of PSA velocity less useful. If the introduction of population screening for prostate cancer were to be considered in the future, reliability of PSA measurements will be of paramount importance.

Currently, the most promising development in PSA measurement is the recognition that the proportion of ‘free’ PSA, not bound to the two proteins alpha-1-antichymotrypsin and alpha-2-macroglobulin, is lower in men with prostate cancer than in those with benign disease. It has been suggested that the use of free to total PSA ratio may give improved discrimination compared with total PSA when the latter is in the range 4–10 ng/ml, with a threshold ratio of 0.15 giving optimum sensitivity and specificity. Again, there is further scope for developing an optimum combination of levels of free and total PSA, but the accuracy and repeatability of assays remain crucial.

The potential for over-diagnosis

One potential disadvantage of screening is the detection of conditions which are of limited or uncertain relevance to the health and well-being of the man concerned. This includes the detection of non-progressive lesions and the assignment of borderline lesions as malignant. The extent to which routine screening would result in over-diagnosis remains a question of debate. It has been known for many years from autopsy studies that many men at death have undiagnosed prostate cancer, and this has raised concerns that screening might detect a large number of otherwise ‘latent’ cases. The issue of non-progressive disease is considered here.

One problem with screening for prostate cancer using the PSA test is the possibility that a significant number of the cancers diagnosed might not have caused problems during a man’s lifetime, had they been left undetected. This, compounded with the potential morbidity caused by treatment of screen-detected disease, raises concerns about the cost-benefit ratio of screening, even if screening were shown to be effective in reducing mortality from prostate cancer.

The major prognostic factors for prostate cancer at present are stage and histological grade, usually measured by the Gleason score, which is an indicator of malignant potential (Table 1). Several investigators have claimed that the majority of prostate cancers detected by PSA screening are ‘clinically significant’ and, therefore, that screening will not result in extensive over-diagnosis. For example, in one study of 100 screen-detected
Table 1 Staging prostate cancer by Whitmore-Jewett and TNM classification

<table>
<thead>
<tr>
<th>Description</th>
<th>Jewett</th>
<th>TNM</th>
</tr>
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<tbody>
<tr>
<td>Disease localised to prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental histological finding (TURP)</td>
<td>A</td>
<td>T₁</td>
</tr>
<tr>
<td>Low grade, &lt; 5% specimen</td>
<td>A₁</td>
<td>T₁a</td>
</tr>
<tr>
<td>High grade, &gt; 5% specimen</td>
<td>A₂</td>
<td>T₁b</td>
</tr>
<tr>
<td>Either identified by needle biopsy or involves both nodes</td>
<td>-</td>
<td>T₁c</td>
</tr>
<tr>
<td>Risk recognised clinically</td>
<td>B</td>
<td>T₂</td>
</tr>
<tr>
<td>Tumour confined to 1 lobe</td>
<td>B₁</td>
<td>T₂a</td>
</tr>
<tr>
<td>&gt;1.5 cm: in one lobe with normal prostate on 4 sides</td>
<td>B₁₇₅</td>
<td>T₂b</td>
</tr>
<tr>
<td>&gt;1.5 cm: surrounded on 3 sides by normal tissue</td>
<td>B₁₀₂</td>
<td>T₂c</td>
</tr>
<tr>
<td>&gt; 1.5 cm or tumour in both lobes</td>
<td>B₁₀₅</td>
<td>T₂d</td>
</tr>
<tr>
<td>Periprostatic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extension beyond prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral extension</td>
<td>C₁</td>
<td>T₃</td>
</tr>
<tr>
<td>Seminal vesicle extension</td>
<td>C₂</td>
<td>T₃a</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td>T₃b</td>
</tr>
<tr>
<td>Distant disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated acid phosphatase level only</td>
<td>D₀₂</td>
<td>T₄a</td>
</tr>
<tr>
<td>Pelvic lymph nodes</td>
<td>D₀₇₇</td>
<td>N₀,₁a</td>
</tr>
<tr>
<td>Bones, lung, extrapelvic nodal involvement</td>
<td>D₀₁₇</td>
<td>N₀,₁b</td>
</tr>
</tbody>
</table>

*N₀ no lymph node involvement; N₁ single lymph node, homolateral; N₂ multiple or contralateral lymph nodes; N₃ bulky pelvic lymph nodes; *T₃ penetrates capsule with or without seminal vesicle invasion; and T₄ fixed to periprostatic side wall or adjacent organs.

cases, only 6% were low grade (Gleason score < 5) and 68% had tumour volume > 0.5 ml²¹. However, although PSA testing may be more likely to detect more aggressive disease, the cancer detection rates found in screening series so far suggest that considerable over-diagnosis may still occur. For example, studies from the US have reported detection rates of 3% at initial screen, and of the order of 1% at 6-monthly rescreening²². The higher prevalence:incidence ratio indicated by the detection rates at first screen imply a long average preclinical sojourn time and/or the diagnosis of non-progressive disease. However, more information is required on the natural history of prostate cancer to determine whether a latent or non-progressive form exists, or whether this merely represents one end of the distribution of growth rates. At present, it remains unclear what proportion of screen-detected cancers would eventually progress and cause morbidity and/or mortality. Most screening studies reported to date have been based on volunteers or selected populations, and lack information on long-term follow-up²⁹,²²–²⁴. Results from population-based screening trials, in progress or planned, are needed to provide accurate data not only on detection rates and the prevalence:incidence ratio, but
also on what happens to incidence rates in the screened population, both during rescreening and after screening has been completed. Comparison of the cumulative incidence rates in the study and control groups will allow an accurate estimate of the extent of over-diagnosis to be made.

The challenge for future research is to develop methods to differentiate between progressive and non-progressive disease, either by refinements of the PSA test with the use of different measurements or secondary diagnostic tests to determine whether a screen-detected case warrants radical treatment. At present, tumour grade is the best indicator of progression, but the question of whether tumour grade changes over time has not yet been resolved. Data from randomised trials will provide further evidence on the disease natural history.

**Treatment issues**

One of the prerequisites for the introduction or recommendation of screening is that there should be an available treatment for screen-detected disease. Most prostate cancers detected by routine screening will be localised (Stage T1–T2, Stage A or B; Table 1). Some may be locally extended, and a few may be metastatic. The three main choices of treatment for localised cancer are watchful waiting, radical prostatectomy and external beam radiotherapy. Problems arise with screening due to a lack of evidence regarding the effectiveness of radical treatment, whilst it is not clear that there will be any advantage for cancer detected by screening if management is by surveillance only.

Each treatment has advantages and disadvantages. Watchful waiting involves monitoring the progress of the cancer using PSA, digital rectal examination, a record of symptoms, and, where indicated, transrectal ultrasound to monitor local progression as well as bone X-rays and other imaging or biochemical tests. Active treatment is only employed if the cancer appears to progress in stage or to cause symptoms. The advantages are that many men outlive their cancer and die of other causes, so avoiding the side-effects and complications of radical treatment which include incontinence, and impotence. The disadvantages are that some men will go on to develop metastatic disease with all the distress and complications that this will cause. There is also the anxiety associated with the knowledge of having a cancer which is not being treated.

The detailed natural history of untreated prostate cancer remains unclear. Follow-up studies of series of untreated cases provide conflicting results: they are difficult to compare because of different age, stage and grade distributions of the cases, and cannot be readily generalised to cases detected by screening.
Radical prostatectomy involves the removal of the whole prostate gland, without damaging the adjacent neurovascular bundles, by abdominal or perineal surgery. The advantages are that it may provide complete cure of the cancer. The disadvantages are the complications arising from the surgery, the discovery of disease that is not localised and thus may not benefit from surgery, and unnecessary radical treatment of a disease which may never have progressed. Estimates of complication rates vary between studies, but some from the US show 20% of men with non-intermittent incontinence after treatment, over 60% with impotence, and <1% peri-operative mortality. Developments which may help to improve survival or delay progression following radical prostatectomy include: pre-operative endocrine therapy; adjuvant hormone therapy for cases with lesions revised to a more severe stage following surgery; and improved case selection for surgery to identify patients with organ confined disease and to avoid over treatment of insignificant tumours.

External beam radiotherapy focuses on the prostate gland plus or minus the seminal vesicles. The advantages are that it can be tolerated by men of varying health and fitness. The disadvantages include complications arising from the procedure, difficulty in monitoring subsequent progress because of damage to surrounding tissues, as well as inaccurate clinical staging and treatment of a disease which might not have been life threatening. Complications include 6.1% with any incontinence, 41% with impotence, 4.5% with urethral stricture, and 2.3% with bowel damage. New developments may well help to improve the outcome of this mode of treatment, including conformal radiotherapy downstaging by anti-androgens to reduce the size of the tumour, adjuvant hormone therapy following radiotherapy, and interstitial radiotherapy.

There are no results available from randomised controlled trials regarding the effectiveness of different treatments. Two trials comparing radical prostatectomy with watchful waiting are now underway in Scandinavia and the US but it will be several years before results become available. In the UK, randomisation of patients into trials of treatment has proved difficult due to patient and clinician preference.

Many non-randomised studies have compared the three modes of treatment but the results are often difficult to interpret because of concerns about biases arising from the selection of patients, and variation in methods and periods of follow-up. One overview of watchful waiting concluded that this was a reasonable choice for some men with grade 1 or 2 clinically localised disease and a life-expectancy of 10 years or less taking co-morbidities into account. Similar conclusions were drawn in a decision analysis comparing the three modes of treatment taking into account a measure for quality of life.
Radical prostatectomy or external beam radiotherapy were thought to benefit men aged 65 years or less with moderate to high grade tumours. More recently, a report of cases analysed by ‘intention to treat’ in the US showed that the survival benefit from radical prostatectomy may have been slightly exaggerated in previous studies which studied only treated patients but, nevertheless, this treatment seems to benefit men even with clinically localised grade 3 tumours.

New hopes for the future lie in molecular biology: to identify the cancers that are most likely to progress and would benefit from treatment, and to develop treatments that can specifically target certain functions or points in the cell cycle of the cancer cells. For example, it has recently been shown that the induction of apoptosis by external beam radiotherapy or by hormone therapy may be blocked in patients whose tumours have p53 mutations.

Until results of randomised trials become available, clinicians need to help patients make an informed choice of treatment. The current choice of treatment depends mainly on information from clinically based research, as well as personal experience and expertise. The choice varies markedly between countries and between consultants within countries. In the US, radical treatment by prostatectomy is the preferred option whereas in Europe, and Scandinavia, watchful waiting is the first choice. If screening and radical treatment were shown to be effective, countries such as the UK would need considerable extra resources for the management of screen-detected disease.

The effectiveness of screening

Implementation of population screening for prostate cancer requires demonstrable benefit in terms of reducing mortality from prostate cancer. At the present time, this benefit has not been adequately established. The ‘gold standard’ for demonstrating effectiveness is a randomised controlled trial; other measures, as discussed below, provide supporting but not conclusive information.

It is clear that screening by PSA can detect asymptomatic disease, and current evidence suggests that this will lead to an increasing proportion of earlier stage cancers among screen-detected, as compared with clinically detected, cases. Data on survival indicate an improved prognosis with diagnosis at an early stage; for example, data from the Thames Cancer Registry show 5 year relative survival rates of 72% for localised cases compared with 19% for metastatic cases. However, it cannot be concluded from these findings that screening will necessarily result in a reduction in either the incidence of metastatic disease or...
mortality from prostate cancer. There are few published data on the survival of prostate cancer cases detected by screening. In any case, comparisons of survival will be affected by lead-time bias, which is the increase in length of survival by the time by which diagnosis is advanced, regardless of any impact on time of death, and by length-bias, which is due to the increased chance of detecting slower-growing cancers which may also have a better prognosis.

A case-control study, in which the history of screening by digital rectal examination in 139 cases of metastatic prostate cancer and matched, disease-free controls was compared, found little apparent effect of screening, with a relative risk of 0.9 of metastatic disease in men with one or more screening examinations compared to those with none, after adjustment for racial differences. Again, however, results of such studies need to be interpreted with caution, particularly due to the possible effect of selection bias, whereby those men screened may be at a different underlying risk (either greater or lesser) than those not screened.

It has recently been shown that mortality from prostate cancer in the US has started to fall, and it has been claimed that this may be attributable to earlier diagnosis and screening. However, others have argued that there is no correlation between the size of mortality reduction and either the level of screening or the resulting increased incidence in different states.

A true estimate of the effectiveness of screening in reducing mortality from prostate cancer must, therefore, await the results of randomised controlled trials. Trials are currently in progress in the US and Europe, although not in the UK.

The financial costs of screening for prostate cancer have not been precisely estimated. Most studies suggest that the cost of detecting one prostate cancer through screening may be less than for other cancers; in one UK pilot study, the cost of detecting one prostate cancer using PSA and digital rectal examination in a general practice setting was estimated to be £1,654. However, in the light of the uncertainties surrounding the effectiveness of screening, the value of the several models which have been developed to estimate the cost-benefit of prostate cancer screening is debatable. All necessarily make assumptions about the natural history of the disease and the effectiveness of treatment which only randomised trials can answer. The financial costs of screening may be offset, in part, by reduced costs of treating metastatic disease. Other ‘costs’ or disadvantages of screening need to be considered, including the extent of increased morbidity due to over-diagnosis and treatment complications as discussed above, as well as the potential psychological impact of screening. One adverse affect of screening may be increased anxiety, notably among those recalled for further investigation following a
positive test, but also at other stages of the screening process. There will also be psychosocial factors associated with the problems of overdiagnosis and the effects of radical treatment. Any man with screen-detected cancer who does not benefit in terms of time of death merely lives longer both with the knowledge of having cancer and with the side-effects of treatment, but, even in those who benefit from screening, these factors must be taken into account.

Guidelines and recommendations

There is increased pressure for guidelines and recommendations on screening for prostate cancer. Organisations which do not currently recommend routine screening include the US Preventive Services Task Force\(^46\), the Canadian Task Force\(^47\), the Cancer Society of New Zealand, the National Health Committee of New Zealand, the Australian Health Technology Advisory Committee\(^48\), the Executive of the Urological Society of Australasia, and the World Health Organization\(^49\). Two reports commissioned by the National Health Service for England and Wales\(^8,50\) and a summary by the NHS Centre for Reviews and Dissemination\(^51\) also do not support general population screening without evidence from a randomised controlled trial.

In contrast, the American Urological Association and the American Cancer Society\(^52\) have both recommended screening for men aged 50 years and over. The latter proposed annual screening for men with ‘average risk’, but in the same document recognized that there had been no randomized controlled trial of screening demonstrating a reduction in mortality. In a subsequent revised set of guidelines\(^5\), the American Cancer Society recommended that both the PSA test and digital rectal examination should be offered annually, beginning at age 50 years, to men who have at least a 10 year life expectancy and to younger men who are at high risk. Information should be provided to the men regarding potential risks and benefits of screening.

For a country such as the UK, there are effectively two questions. Should population-based screening for prostate cancer be recommended and introduced nationally? What advice about screening for prostate cancer should be given to individuals consulting their family doctor? The first question is the simplest to answer. Few would argue that there is sufficient evidence on the effectiveness of screening to propose a national policy, with the ethical implications of encouraging participation of healthy men in a programme with no proven benefit and some potential harm. On an individual basis, the solution is less clear. Current recommendations to GPs in this country stress the need to
inform men inquiring about PSA testing of the potential benefits and costs of testing, investigation and treatment. Even for the small percentage of men at possible increased risk due to family history, the optimum management is not known.

Recommendations, however, may not always reflect what happens in practice. In the US, a nationwide survey in 1995 showed that 87% of urologists and 76% of primary care physicians ‘almost always’ requested a PSA test as part of the diagnostic evaluation of men older than 50 years with symptoms suggesting a diagnosis of benign prostatic hypertrophy (BPH). The proportion of primary care physicians who reported requesting a PSA test as part of health maintenance varied with the age of the patient but was as high as 53% in men aged 80 years or more, most of whom would have a life expectancy of less than 10 years.

In New Zealand, a random survey of 317 family doctors found that about 50% routinely screened some of their male patients aged 50 years or more with PSA and digital rectal examination, including two-thirds of those who reported that they believed the test to be ineffective. About 70% of GPs left the decision about the effectiveness of screening up to their patients and only 5% said that they would refuse to offer a questionable screening test to their patients.

In the UK, a much lower proportion of men are likely to be offered PSA by their family doctor than in the US, but the proportion is likely to increase through increasing pressure from the media, public and companies preparing the PSA test kits. In the US, public pressure to be screened is likely to be high.

Conclusions

There is an understandable impatience from urologists in the UK who are unwilling to wait the 10 years or more needed before results from randomised controlled trials of screening become available. However, the potential disadvantages highlighted above mean that evidence from such trials is essential, and that attempts to predict the effect of screening from other data are likely to be subject to bias. The danger is that, if the use of PSA testing continues to increase unchecked, it will become impossible to conduct a randomised trial, either because of the practical difficulty of finding an unscreened control group or because it will no longer be thought ethical to ‘deprive’ a control group of an intervention thought to be beneficial. The situation will then become akin to that for cervical screening, where evidence of benefit is derived largely from geographical and time trend comparisons, but it is difficult to estimate the magnitude of an effect due to screening.
Acknowledgements

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