IS PROSTATE CANCER SCREENING BENEFICIAL?

Screening is a multidisciplinary science involving scientists and clinicians with a wide range of expertise. At The Institute, collaborations between the Department of Health's Cancer Screening Evaluation Unit and colleagues in other Institute research sections and the Royal Marsden enable our studies of prostate cancer screening to address many of the concerns surrounding this controversial issue.

From left to right, Sue Moss, Jane Melia, Maggie Watson, Clare Moynihan and Penny Coulson.

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Whether screening for prostate cancer ultimately leads to fewer deaths from the disease is currently unknown. There is an urgent need to evaluate the screening process in order to establish the best pathway from the initial identification of target populations, through testing, to the choice of treatment and minimisation of complications.

Prostate cancer on the increase

Prostate cancer is now the most frequently diagnosed cancer in men in England and Wales, with just under 25,000 newly diagnosed patients in 2000, the majority of whom were over 65 years of age. Over time, the incidence rates have risen in many developed countries. This trend may be attributable to changes in lifestyle and exposure to environmental factors, but it is also highly likely that the increased detection of the disease is due to the greater use of prostate specific antigen (PSA) testing, in which the level of PSA in the blood is measured as a marker of prostate cancer.

Controversy surrounds the use of the test, however, as it may detect prostate cancers which, if left untreated, would never cause the individual harm. Yet many of these men nevertheless receive treatment, which often causes considerable side effects.

On the other hand, the increased use of the PSA test is likely to have led to an increase in the proportion of prostate cancers diagnosed at an early stage. This, along with the improved treatment of early stage disease, could explain why mortality rates started to decrease in several developed countries during the 1990s. In 2002, there were still almost 9,000 deaths in England and Wales – but, thankfully, far fewer men die from prostate cancer than are diagnosed with the disease.

Can prostate cancer be prevented or cured?

Ideally, it would be best to prevent men developing prostate cancer in the first place. But currently the causes of prostate cancer are unknown. A second option would be to cure the disease once it is diagnosed. However, for about a third of cases, the disease is fairly advanced at diagnosis and there is no cure at this late stage. Moreover, it is difficult to detect early stage prostate cancer as there are no specific signs or symptoms.

Therefore there has been great interest in screening to try and reduce prostate cancer

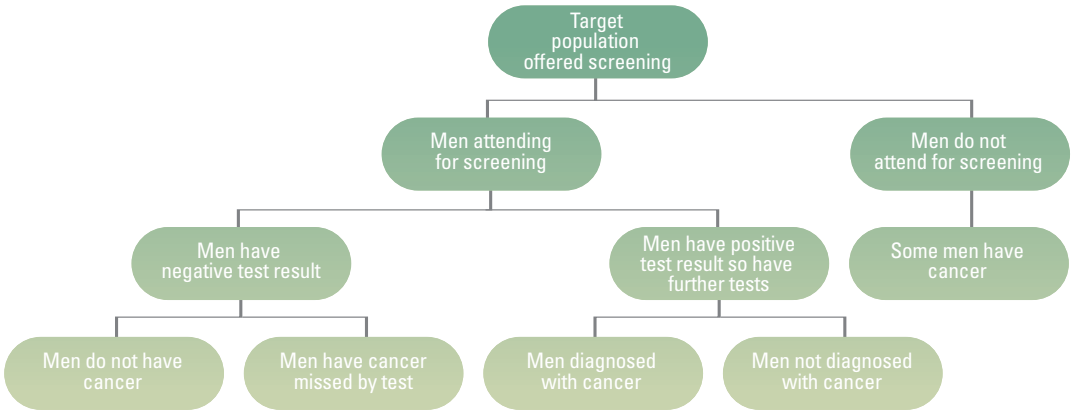

Figure 1
A screening pathway for the PSA test.

mortality and to prevent serious complications associated with advanced disease such as urological malfunction, bleeding and obstruction, and bone pain.

What is the case for prostate cancer screening?

It is important to note that there are many concerns about prostate cancer screening:

- There is no conclusive evidence that screening reduces mortality;
- There is considerable over-diagnosis of cancers which would otherwise not have been life threatening;
- There is wide variation in the rates of prostate cancer progression: slow growing cancers may not need treatment but fast growing cancers need to be treated promptly;
- Both over-diagnosis and the treatment of slow growing cancer may result in over-treatment and reduced quality of life;
- Progression cannot be accurately predicted;
- There is no conclusive evidence for the best choice of treatment.

Yet, despite the uncertainties about the benefits of screening, increased media attention, public awareness and concerns among both the general public and the medical profession about missing the opportunity to diagnose the disease when it is potentially curable have all led to an increase in screening in England and Wales.

Because more men are asking about the PSA test, in September 2000 the NHS developed the Prostate Cancer Risk Management Programme, designed so that any man considering having a test is given balanced information to enable him to make an informed choice about whether or not to proceed.

Even if a screening programme was introduced to determine whether PSA testing is beneficial, the uptake rate of screening and the accuracy of the test will affect the proportions of men with different outcomes (Figure 1).

Furthermore, if the research trials currently underway do eventually show that population screening leads to a reduction in the number of deaths from prostate cancer, it will be necessary to weigh up the benefits and disadvantages of screening (Figure 2).

Clearly, there are many unresolved questions about the effectiveness of prostate cancer screening. At The Institute, however, it is exactly these issues which the Cancer Screening Evaluation Unit (CSEU), in the Section of Epidemiology, sets out to address.

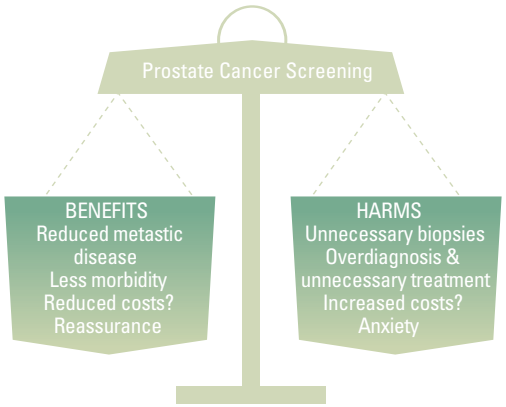

Figure 2 Weighing up the benefits and harms of screening for prostate cancer.

Studies at The Institute to evaluate screening

The remit of the CSEU is to conduct studies to:

- evaluate the effectiveness of existing screening programmes and the possible value of screening where there is not yet proven benefit;
- investigate specific aspects of screening or the natural history of disease.

A few of our current studies that are evaluating aspects of prostate cancer screening are outlined below.

Effect of screening on prostate cancer mortality

Dr Sue Moss, the Unit's Associate Director, is heading the analysis of a large European trial of prostate cancer screening, called the European Randomised Study of Screening for Prostate Cancer (ERSPC). Seven centres – in Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden and Switzerland – are currently participating, with the target of recruiting over 180,000 men in the core age group 55–69 years from the general population. The trial will compare men randomised to be offered screening with men in a control arm, not being screened, to find out whether early detection and treatment of prostate cancer reduces the number of deaths from prostate cancer. Results on mortality are expected in 2008, however interim results have already been published on a range of outcome measures including detection rates, progression rates and psychosocial effects.

Targeted screening for familial prostate cancer

A study, led jointly by Professor David Dearnaley, in the Urology and Testicular Cancer Unit, and Dr Jane Melia in the CSEU, is investigating whether the targeted approach of offering screening to high risk families is feasible. Male first degree relatives, mostly brothers, of men diagnosed with prostate cancer under the age of 65 years are being offered PSA screening. We are studying the uptake rate of screening, reasons for non-participation and positive predictive value of the PSA test (proportion of men with a positive PSA test found to have cancer on biopsy). Clare Moynihan will investigate the psychosocial effects of screening. This collaborative project, funded by Cancer Research UK, involves colleagues in:

- The Institute's Academic Radiotherapy Department;
- The Institute's Section of Cancer Genetics – anonymised blood samples are being stored for future genetic testing in the Familial Prostate Cancer Study led by Dr Ros Eeles;
- Psychological Medicine at the Royal Marsden;
- National Cancer Research Networks.

Rate of PSA screening – an example of ad hoc testing in the general population

So that the NHS can plan the provision of services, it is important to know how much screening is taking place and how patients are being managed. Although there are data available to study the overall rate of PSA testing, the reasons why each test is undertaken are not standardly recorded. Therefore Dr Melia led a study, funded by the Department of Health, to investigate the rate of PSA testing associated with prostate cancer screening and associated with other reasons. The results from more than 330 general practices in England and Wales confirmed that the rate of testing is increasing, but it is low compared with the rate in the USA, and that the rate of screening varies greatly between different sections of the population.

Assessing which prostate cancers will progress

The CSEU has helped to coordinate a pathology panel, led by Dr Connie Parkinson at University College, London, and funded by the Prostate Research Campaign UK, to investigate the reasons for observer error in the pathological grading of prostate cancers identified by biopsy. A prostatic biopsy is performed if a man is found to have a raised PSA level. The removed tissue is examined by a pathologist to confirm if cancer is present. Importantly, the pathologist also reports the grade of the cancer, which is subsequently used to decide patient management. However, grading is becoming difficult because screening is resulting in an increasing number of small cancers being diagnosed.

Future research and developments

Even if it is shown that screening has the overall effect of reducing prostate cancer mortality, patients and healthcare professionals may still be concerned about the risks of over-diagnosis and over-treatment. Therefore, future research priorities should be focused on assessing these risks (Table 1).

Our current studies will address some of these concerns. Analysis of data from the European trial will allow the CSEU to contribute evidence to resolve the question of whether or not screening is beneficial. We will continue to respond to the needs of the Department of Health and NHS by investigating the extent and characteristics of ad hoc testing. We are also assisting with the development of an external quality assurance scheme for prostatic biopsies. This project, funded by the NHS Cancer Screening Programmes office, is led by Dr Pat Harnden at St James' University Hospital, Leeds.

Collaborative work, extending across Institute and Royal Marsden departments, will consider many of the other priorities.

Institute scientist Professor Colin Cooper coordinates one of two National Cancer Research Institute prostate cancer research collaboratives in England and Wales, which aims to develop research in molecular pathology, therapies and aetiology.

Genetic epidemiology is at the core of The Institute's scientific strategy to develop rapid and effective translation of cancer genetics to patient care and cancer prevention. Thus, The Institute is in a prime position to develop and evaluate genetic approaches to screening to ensure a more targeted way of identifying specifically which men should be screened and which men need treatment.

> Our hope is that if the large, long term trials report a reduction in prostate cancer mortality, other research findings will ensure that future screening programmes are efficient as well as effective not only at reducing mortality but at maintaining manageable levels of workload within the NHS and an acceptable level of quality of life for the individual.

Table 1
Future research priorities in prostate cancer screening

- To evaluate whether screening gives benefit
- To improve the accuracy of the screening test
- To identify high risk groups by genetic markers to inform targeted screening
- To improve the accuracy of pathological grading used to decide treatment
- To identify markers of progression used in decisions on treatment
- To improve methods of monitoring progression
- To reduce the proportion of men experiencing long term side effects from certain treatments
- To monitor ad hoc testing nationwide to plan NHS services