

2

Trends in Prostate Cancer Screening: Overview of the UK

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CONTENTS

WHAT HAPPENED IN THE UK SINCE THE INTRODUCTION
OF PSA TESTING?

REFERENCES

SUMMARY

There is a continuing lack of evidence that screening for prostate cancer results in a significant improvement in survival and/or quality of life of men with the disease. Moreover, there is a growing concern that the introduction of a national prostate cancer screening programme might result in over-diagnosis of men with “clinically insignificant” or “indolent” prostate cancer who could be harmed by unnecessary treatments. To date, systematic screening for prostate cancer has not been introduced as a public health policy in the United Kingdom, and the rate of opportunistic prostate-specific antigen (PSA) testing remains low compared to countries in Western Europe and in the USA. The UK Department of Health guidelines recommend that when an asymptomatic man requests PSA testing, he should be counselled regarding the controversies and uncertainties surrounding prostate cancer screening and treatment, and PSA testing should proceed only once he is able to make a fully informed decision. Several randomised controlled trials are in progress in Europe and the UK and will shed new light on whether or not PSA-based screening for prostate cancer offers more benefit than harm. Until such data become available, the responsibility of the urological community at large is to inform appropriately men who are seeking screening and to prevent over-diagnosis and over-treatment of this common but ubiquitous malignancy.

Key Words: Prostate cancer, Screening, United Kingdom, Prostate-specific antigen (PSA).

Prostate cancer is an important health problem in the UK. In 2004 there were almost 35,000 new cases of prostate cancer diagnosed and each year around 10,000 men die from this disease alone (1). It is now the most commonly diagnosed male malignancy

and the second most common cause of male cancer related death in the UK. The incidence has increased during the late 1980s and 1990s, as in many other Western countries, largely as a result of prostate-specific antigen (PSA) testing. The mortality rate from prostate cancer peaked in the early 1990s in the UK and the age-adjusted mortality rate has subsequently declined over the last 15 years for reasons that as yet remain unclear (2). This reduction in prostate cancer mortality since 1992 has been less pronounced in the UK compared with the USA (3). The US reduction coincided with the widespread uptake of PSA testing in that country, but whilst this might indicate an early effect of initial screening rounds on men with more aggressive but asymptomatic disease, there is still no conclusive evidence to support the concept that PSA-based screening decreases prostate cancer-specific mortality (4). The recent differences between the USA and UK in rates of decline in prostate cancer-related mortality may also be attributable to other factors such as different approaches to detection or prostate cancer treatment.

Proponents of PSA-based prostate cancer screening in the UK include members of the general public, the media, and the medical profession, however, at present, the merits of introducing a national prostate cancer screening programme in the UK are unclear, and the evidence to support such a programme remains insufficient. In the absence of robust data from randomised controlled trials (RCTs) indicating a survival benefit for men who undergo prostate cancer screening compared with men who do not, it would be inappropriate to introduce such a programme on a national scale. The situation appears somewhat different in the USA, where the American Urological Association and the American Cancer Society both recommend screening men over the age of 50 for prostate cancer. In order for a disease to qualify for a screening programme it should meet several criteria as defined by Wilson and Jungner (5) (Table 1). These valid principles have so far guided the debate on the introduction of a national prostate cancer screening programme in the UK.

The aim of any “screening” programme is to use an appropriate test to identify cases, within a population at risk, before clinical symptoms or signs are present, rather than the disease being diagnosed at a later and more advanced stage when symptoms or signs have become apparent. In the case of cancer, the assumption is that either the malignancy or a precursor lesion may be detectable during a “latent” period prior to clinical

Table 1
Wilson and Jungner Criteria for Mass Screening for Any Disease

1	The condition is an important health problem
2	There is adequate knowledge of the natural history of the condition, with a recognised latency period or early symptomatic stage
3	There is a simple, safe, acceptable, precise, and validated screening test
4	There is an agreed policy on the further diagnostic intervention
5	There is an effective treatment or intervention
6	There are evidence-based policies covering who to treat and how to treat
7	There is evidence from high-quality RCTs that screening reduces mortality or morbidity
8	There is evidence that the complete screening programme (i.e. test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable
9	There is evidence that overall benefit from the screening programme outweighs the physical and psychological harm

manifestation. The over-riding aim of any population-based screening programme is to reduce cancer morbidity and mortality caused by the disease, based on the premise that early diagnosis and treatment improves both prognosis and survival. Prostate cancer may be detected at an early stage in men by performing a serum PSA test followed by a prostate biopsy, and patients with organ-confined prostate cancer may be cured by either radical prostatectomy or radical radiotherapy. Because of significant lead-times to the development of life-threatening disease, and the recognised stage-migration caused by screening, many cancers are not likely to cause harm to men who harbour the disease. “Over-diagnosis” and subsequent “over-treatment” of disease which does not need to be cured could therefore prevail as a consequence of systematic screening, in the absence of tests which can discriminate between potentially harmful and clinically insignificant cancers.

Current experience and controversies surrounding prostate cancer screening in the UK are discussed below.

WHAT HAPPENED IN THE UK SINCE THE INTRODUCTION OF PSA TESTING?

A small scale study of screening acceptability was performed in the UK in the late 1980s, which demonstrated that men in the community will attend for PSA testing if invited (6). As PSA testing became widely available in the following years, the Department of Health discouraged the use of PSA testing for prostate cancer screening, until the late 1990s. In 1995, the Health Technology Assessment (HTA) programme commissioned two systematic reviews of the literature, which clearly stated that there was insufficient evidence to recommend mass-screening for prostate cancer as a public health policy (7,8). The reviews recommended that urgent research into screening and treatment of prostate cancer should be undertaken in the form of large RCTs. Subsequently, HTA issued a call for primary research in this area, and commissioned the feasibility phase of the ProtecT (*Prostate testing for cancer and Treatment*) study, followed by the full trial in 2001 (9,10). The ProtecT study is currently the largest randomised controlled trial of treatment effectiveness in prostate cancer worldwide. The feasibility phase demonstrated that screening was acceptable amongst British men, and that the majority agreed to be randomised to a three-arm trial of active monitoring, radical prostatectomy, and 3-D conformal radiotherapy. The main trial started in 2001, and aims to test 130,000 asymptomatic men aged 50–70 years over a period of 5 years. Of those, 1,800 patients with clinically localised prostate cancer will be randomised to active monitoring, radical prostatectomy, or radiotherapy. The primary end-point will be survival at 10 years, with a number of secondary end-points including detailed quality of life analyses. The study has been extended through further support from Cancer Research, UK and the Department of Health to include the evaluation of case-finding. This effectively converted the ProtecT study into the intervention arm of a clustered randomised trial of screening. Recruitment to the study is near completion, and results will become available within the next decade, at the same time as the other much awaited screening studies in Europe and the USA.

By the year 2000, the UK Department of Health recommended that if a man requested PSA testing to be screened for prostate cancer, careful counselling should be given regarding the uncertainties surrounding the diagnosis and treatment of the disease, and

PSA testing should be performed only after the man is fully informed and able to make such a decision.

Despite the absence of a proven benefit from PSA-based prostate cancer screening recent years have seen a modest rise in the number of men undergoing ad hoc PSA-test screening in the UK. A study in England and Wales suggests that the annual rate of PSA testing in men aged 45–84 years without a previous prostate cancer diagnosis is approximately 6% (11), which remains low compared to rates of testing in Western Europe and in the USA where a recent estimate suggested testing rates of over 25% in men aged 50–75 years (12). A recent pilot study of screening in a younger age group of men between 45 and 49 years embedded in the UK ProtecT study not only showed a lower uptake of testing in these men compared with the older population, albeit in the context of an RCT, but also demonstrated that clinically significant cancers occur in these younger men (13).

The “lead-time” for a cancer is the length of time by which the date of diagnosis is advanced through screening from the date it would have been diagnosed clinically. For prostate cancer the lead-time using PSA testing ranges from 5 to 14 years depending on the grade and stage of the disease (14–18). The decline in mortality seen in the UK since the early 1990s is therefore unlikely to be attributable to PSA testing as the effect has appeared too early, given the long lead-time involved in the progression of prostate cancer. For instance, only a small proportion of men with early stage prostate cancer would be predicted to die from this malignancy over the next 20 years in the absence of screening even when treated conservatively (19). Although PSA testing became widespread in the USA in the late 1980s and early 1990s, the reduction in mortality occurred too quickly to be attributed to early detection alone (20,21), whilst the reduced mortality seen in the UK coincided with a period where PSA testing and aggressive treatment for prostate cancer was considerably more limited. It is likely that hitherto unidentified factors other than increased detection and radical treatment of early-stage prostate cancer account for the decline in prostate cancer mortality witnessed in the UK since the early 1990s. This has been particularly apparent in men aged 55–74 years but has also been witnessed to a lesser degree in men aged over 75 years. Potential explanations for this reduction in prostate cancer-specific mortality since the early 1990s include increasingly radical therapy amongst younger men with localised or screen-detected low-volume disease, effects of stage migration, and more widespread use of medical androgen suppressing therapies and aggressive treatment of early locally advanced disease.

Current knowledge of the natural history of prostate cancer is limited to clinically diagnosed cases, whilst very little is known of the natural history of cases of screen-detected prostate cancer, although this is likely to improve in the near future following the results of randomised clinical trials on both sides of the Atlantic (22,23). Given that clinically detected prostate cancer often remains indolent or progresses very slowly and thereby may be considered “clinically insignificant”, it is likely that a substantial proportion of men in the UK who may be found to have screen-detected prostate cancer would never develop clinically significant disease. A recent study suggests that over half of all men eligible for expectant management are actually over-treated in the USA (24). Indeed, it is likely that many men in the UK with screen-detected prostate cancer would die of competing morbidity, and it has been estimated that only around one in eight cases of screen-detected prostate cancer would cause mortality if left untreated (25). Prostate cancer screening would primarily detect organ-confined disease, and it is

presently difficult to differentiate between indolent organ-confined cases, which could undergo active surveillance, and high-risk or potentially aggressive cases which would merit active intervention (26).

Despite the persistent lack of evidence, recent guidelines from the UK National Institute for Clinical Excellence (NICE) recommend that men with low-risk prostate cancer should first be offered active surveillance, a view contested by the British Association of Urological Surgeons, which recommends that men with perceived low-risk disease should be explained the uncertainties around treatment, and offered active surveillance alongside radical interventions in order to make an informed decision regarding management of their disease (27). It is hoped that improved risk stratification, based on novel biomarkers in clinical samples, may enable improved targeting of radical treatment to those men with organ-confined prostate cancer at risk of rapid progression. The development of a “molecular signature” for risk stratification of prostate cancer cases is warranted in combination with nomograms, which together may enable more accurate risk assessment of clinically localised disease in the future (28).

A screening test should ideally have a high sensitivity, specificity, positive predictive value, and negative predictive value. The level of serum PSA used as a threshold to separate cases of the disease from men without prostate cancer is controversial. For instance, the Prostate Cancer Prevention Trial demonstrated that a significant proportion of asymptomatic men with a PSA less than 4 ng/mL may harbour a prostate cancer detectable by prostate biopsy (29). There is therefore no PSA threshold below which an asymptomatic man can be told confidently that he does not have prostate cancer, and furthermore, no test can reliably differentiate “indolent” from clinically significant disease, making reliable treatment decisions difficult to reach. Paradoxically, a raised PSA test does not necessarily mean that the individual has prostate cancer, whilst a “low” PSA value does not eliminate the possibility of an underlying prostate cancer (30,31), and the debate regarding the use of PSA testing in the UK as a screening tool must also consider the acceptability of performing large numbers of prostate biopsies, a substantial proportion of which will not detect a malignancy. A reduction in the PSA threshold used to trigger a prostate biopsy would increase both the number of cancers detected and the negative biopsy rate, and this may result in the PSA test being unacceptable in the context of a screening programme as demonstrated by Roddam et al. (32), on behalf of the UK Prostate Cancer Risk Management Group. Lowering the PSA threshold to 2 ng/mL would increase the number of referrals from 110 to 230 per 1,000 men tested with an increase in the cancer-detection rate from 3.6% to 5.8% in the UK. As the extra cancers detected are likely to be clinically localised, with no evidence that their treatment improves the outcome of the disease, such changes do not appear to be justified at present. Two large RCTs investigating the effects of prostate cancer screening are currently in progress in Europe (ERSPC) and in the USA. (the Prostate, Lung, Colon and Ovary trial) and their results are eagerly awaited (22,23).

There is a paucity of studies investigating the psychological impact of repeat testing and biopsies for prostate cancer, the anxiety generated by the suspicion of cancer diagnosis, and the associated cost to society. The appropriate course of action in men with a raised PSA who are not found to have prostate cancer on an initial biopsy remains unclear, and must be taken into consideration in the prostate cancer screening debate.

The UK health providers have consistently taken the view that evidence of treatment effectiveness in screen-detected prostate cancer and benefits of screening must be

provided first, in order to inform public health policy. Very few RCTs have been performed to directly compare the outcomes of the various treatment options for men with organ-confined prostate cancer. An important study in Scandinavia comparing “watchful waiting” with radical prostatectomy for early-stage prostate cancer demonstrated for the first time a survival benefit and a reduced rate of disease progression for men undergoing surgery (33), however, the majority of cases in this study were not representative of screen-detected disease. It is hoped that the UK ProtecT trial described earlier in this chapter, and the US Prostate Cancer Intervention Versus Observation Trial (PIVOT) comparing radical prostatectomy with expectant management for all-cause mortality (34), will inform clinicians and public health policy-makers of the effectiveness of these treatments for screen-detected localised disease.

Today, the likelihood of harm from prostate cancer screening outweighs the prospect of benefit, leading to the inescapable conclusion that screening remains unjustified outside randomised trials investigating its effects. These longstanding dilemmas are being resolved through large robust RCTs supported by governments and funding institutions in the UK and elsewhere, the results of which are awaited eagerly in order to inform public health policy.

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