

# Part 1: The burden of prostate cancer, its natural history, information on the outcome of screening and estimates of ad hoc screening with particular reference to England and Wales

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## INTRODUCTION

There are well established criteria with which the efficacy and effectiveness of screening for a disease may be assessed. A resumé of those of the National Screening Committee is:

- confirmation that the condition is an important health problem;
- knowledge of the natural history of the condition with a recognized latent period or early symptomatic stage;
- implementation of all cost-effective primary prevention interventions;
- a simple, safe, acceptable, precise and validated screening test;
- an agreed policy on the further diagnostic investigation;
- an effective treatment or intervention;
- evidence-based policies covering who to treat and how to treat;
- evidence from high-quality randomized controlled trials (RCTs) that screening reduces mortality or morbidity;
- evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable;
- an overall benefit from the screening programme outweighing the physical and psychological harm;
- proven cost-effectiveness;
- a plan for managing and monitoring the screening programme;
- adequate staffing and facilities.

The reference standard for evaluating the effect of screening on mortality, morbidity and quality of life is a RCT, and in England and Wales, such a trial for prostate cancer was recommended [1]. In this review, the burden of prostate cancer, natural history of the disease including its progression, target populations for screening, choice of screening test, results from studies of screening, effects of treatment and extent of ad hoc screening are reviewed, focusing mainly on publications since 2000 (Appendix 1).

## THE BURDEN OF PROSTATE CANCER

In 2000, prostate cancer became the most frequently diagnosed cancer in men in England and Wales. There were 24 725 newly diagnosed patients registered with prostate cancer (Office for National Statistics, web site for England, and personal communication at the Office for Wales). The overall incidence rate of prostate cancer is 98 per 10<sup>5</sup> men. The incidence rates increase with age; the rate was 5.8 per 10<sup>5</sup> in men aged 45–49 years, rising to 945.8 per 10<sup>5</sup> in men aged ≥85 years. In 2001 in England and Wales there were 8936 deaths from prostate cancer, a mortality rate of 35 per 10<sup>5</sup>. The rate increases with age from two per 10<sup>5</sup> in men aged 45–54 years to 846 per 10<sup>5</sup> in men aged ≥85 years. Most deaths (93%) occur in men aged >64 years, whereas the proportion is lower for incidence (82%).

Prostate cancer is one of the most frequently diagnosed cancers in Western men, with the highest incidence rates being reported in the USA. In 1988–92 the annual incidence rate, age-adjusted to the world standard, was 100.8 per 10<sup>5</sup> in USA white men and 137 per 10<sup>5</sup> in USA black men, using Surveillance Epidemiology and End Results (SEER) data [2]. The lowest rate of 2.3 per 10<sup>5</sup> was reported in Shanghai, China. Genetic factors may explain some of the large differences in incidence among different countries and ethnic groups.

The incidence rate has been increasing in most countries, including those with low rates such as China. Between 1973–7 and 1988–92 the increases were most striking in the USA, Canada, Australia, France and Asian countries [2]. The percentage increases were 25–114%, 24–55% and 15–104% in countries with high, medium, and low initial incidences, respectively.

The rise in incidence in western countries in the 1980s can partly be attributed to the

increased use of transurethral resection of the prostate (TURP) for benign prostate hyperplasia (BPH) and associated increased examination of pathological specimens. During the late 1980s and 1990s testing for prostate-specific antigen (PSA) increased initially in the USA and then in other western countries, both for diagnostic purposes in men with symptoms and in asymptomatic men as a screening test. This will also have been associated with increased examination of biopsy tissue [3]. A true rise in incidence may also have occurred because of changing exposure to environmental factors.

Prostate cancer is also a major cause of cancer death in men in many countries. In 1988–92 the mortality rate age-adjusted to the world standard ranged from 2.8 per 10<sup>5</sup> person-years in Hong Kong to 20.8 in Sweden and 34.3 in US black men [2]. The mortality has increased less than the incidence, but the greatest percentage increase in mortality was in Asian countries. Between 1973–7 and 1988–92, the percentage changes ranged from –3.7% in Sweden to 95% in Singapore. Changes in exposure to causal factors may lead to an increase in incidence and subsequently mortality from prostate cancer. In addition, prostate cancer may be recorded more frequently as the cause of death because of increasing diagnosis and awareness of the disease [4], and changes in the coding of deaths could have contributed to temporal changes.

In the 1990s a decline in prostate cancer mortality was reported in Canada, the USA, Austria, France, Germany, Italy and the UK [5–7]. The cause of the changing mortality rates is probably complex; it was suggested that one factor is the increased use of the PSA test for screening. In the USA, the increase in PSA testing is associated with a decline in both the incidence of distant (metastatic) disease and prostate cancer mortality [7]. However, the pattern of change in mortality is

**TABLE 1** Survival rates for prostate cancer in areas of the south-east of England; showing the 5-year survival estimates (95% CI) for prostate cancer (year of diagnosis 1992–96, follow-up to 2001, Thames Cancer Registry (TCR) area, patients aged <45 years excluded)

Stage or age group	Survival, %
1 (local)	87.4 (86.1–88.5)
2 (direct extension)	61.8 (55.5–67.5)
3 (local nodes)	64.3 (50.4–75.2)
4 (metastases)	25.9 (24.3–27.5)
5 (unknown)	71.3 (69.4–73.1)
Age, years	
45–54	63.8 (58.5–68.7)
55–64	72.4 (70.4–74.3)
65–74	72.9 (71.5–74.2)
75–84	66.3 (64.4–68.2)
≥85	46.8 (42.0–51.5)
Overall	69.5 (68.5–70.4)

inconsistent among countries. In the USA the decline seems to have occurred very soon after the start of PSA testing, and in the UK there was a decline in mortality with no major increase in PSA testing as had occurred in the USA [5]. Other factors which will have contributed to the decrease in mortality from prostate cancer include increased survival resulting from better treatment of advanced disease, which may have delayed disease progression such that men died from other causes [8].

In the USA the lifetime risk of a diagnosis of prostate cancer is ≈16% and the risk of death from prostate cancer ≈3.4% [9]. In a 50-year-old man with a life-expectancy of 25 years, there is a 42% life-time risk of having microscopic cancer, 9.5% of having clinically evident cancer and 2.9% of dying of prostate cancer [10], based on USA data.

## SURVIVAL

In England and Wales, there are no routinely available data to report on the distribution of clinical stage of prostate cancer at the time of diagnosis. In the Thames Cancer Registry (TCR), which covers a population of >14 million, 75% of registrations have clinical stage recorded, and of these 70% are clinical stage 1 (organ-confined). Five-year relative survival rates estimated using the TCR (personal communication, 2003) are given in

Table 1; the rate in men aged ≥45 years has increased from 51.6% in men diagnosed in 1987 to 69.5% in men diagnosed in 1992–96.

## RATIONALE FOR EARLY DETECTION

Early detection may help to reduce mortality from prostate cancer, as a result of early diagnosis, and prevent morbidity from symptoms associated with urological function, bleeding and obstruction, and pain associated with metastases. For men concerned about prostate cancer, a truly negative test will provide reassurance. However, there are likely to be adverse psychological effects, e.g. anxiety associated with the other outcomes of a screening test, i.e. false-negative and false-positive tests, and truly positive tests resulting in a diagnosis of prostate cancer. False-positive tests will also lead to possible adverse effects from further diagnostic investigations such as a biopsy. The benefits of making a diagnosis of cancer at a stage when it is potentially curable must be weighed against the side-effects of radical treatment, and the possibility that the cancer might not otherwise have progressed to become clinically significant [11].

## THE NATURAL HISTORY OF PROSTATE CANCER

One of the major concerns about screening for prostate cancer is that a proportion of the cancers detected may never have become clinically significant, given the slow progression rate of most prostate cancers and competing causes of death in an ageing population. Indeed, autopsy studies show that >30% of men age of >50 years who died from causes other than prostate cancer and with no clinical record of prostate cancer have some cancer in their prostate [12], although the estimate varies according to the thoroughness of the histological protocol used to examine the prostate. Moreover, not all these cancers would have been detected by screening.

Screening has resulted in more cancers being diagnosed while still organ-confined. The challenge is to distinguish between those with limited growth potential, and therefore suitable for active surveillance or conservative management, and those at high risk of local and distant spread. For the latter, the survival benefits of radical treatment may outweigh

the associated side-effects. In addition, some cancers may change from being slow to fast growing, and it is important that this change is detectable so that the course of treatment can be changed while the cancer is still organ-confined and potentially curable.

After the diagnosis of prostate cancer, assessment of prognosis is based on a combination of information, mainly PSA level but also biopsy-derived Gleason grade, cancer volume and imaging. The term 'clinically significant' has been used to describe cancers at risk of progression. However, there is no standardized definition of clinically significant prostate cancer [13–15], nor could there be, given the lack of understanding of the biology of prostate cancer and the need to consider patient-related factors such as age and comorbidity.

The challenge for screening is that the proportion of 'insignificant' cancers detected by the screening test should be low [11]. Estimates of the proportion of prostate cancers detected by screening which would not become 'clinically significant' (i.e. are over-diagnosed) vary from 18% to 85% [16–18,19]. The estimates will vary according to the definition of clinical significance, the characteristics of the men screened, including their age, which round of screening (prevalence or subsequent screen) is being reported, and the time interval between screening rounds.

## PROGRESSION

### LEAD TIMES

Estimates of the lead time (the time by which the date of diagnosis of the disease is advanced by screening from the date when the disease would be clinically diagnosed) range from 5 to 14 years depending on the stage and grade at diagnosis [20–22]. Using random-effects models based on longitudinal data collected for other purposes [21], a lead time of 6.1 years was predicted for localized cancer and 7.7 years for metastatic disease. Using data from the Finnish arm of the European trial [22], the lead time for screen-detected cancer in the prevalence round was estimated as 5–7 years, with a mean duration of a detectable preclinical phase of 10–14 years. Analysis by grade indicated that the lead time for well differentiated cancers is ≈10 years. In that study, the lead time

estimate did not vary by age but in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial [20] longer lead times were associated with lower ages over the age range 55–75 years.

Disease-specific survival associated with screening was estimated using theoretical modelling on data from the SEER database [23]. The authors estimated that screening may advance the date of diagnosis by 9 years. Other reports suggest lead times of 4.5–7 years [24,25,26], although based on different types of data, PSA thresholds and population samples.

#### PROGRESSION RATES

Within any group of prostate cancers, the rate of progression will vary. One measure of the rate of progression is the time taken for the patient's PSA level to double. In a series of patients diagnosed with localized disease, the doubling time was 15–994 months [27]. In a study in the USA, volunteers aged  $\geq 50$  years were screened at 6-month intervals for  $\geq 48$  months [28]; 48% of men whose initial PSA levels were 2.6–4 ng/mL had increased levels ( $>4$  ng/mL) and 13% had cancer detected during the 48-month period. Similar results were reported by Carter *et al.* [29]. Compared with men whose PSA was  $<1$  ng/mL [24], those with a PSA level of 2.01–4 ng/mL were 5.5–8.6 times more likely to develop prostate cancer within 10 years. There are no consistent results from which to conclude that progression rates differ among cancers diagnosed in patients at different ages [30].

#### TARGET POPULATIONS

The choice of screening populations should be determined in part by the frequency of disease in that population, to ensure that a high proportion of cancers are detected without causing unnecessary anxiety to a high proportion of men who do not have the disease. The population being screened should also be expected to increase their life-expectancy with some acceptable level of quality of life. It would be unethical to offer screening which can cause anxiety and other psychosocial effects to a population with a short life-expectancy as a result of their age or comorbidity.

Screening may be offered to the general population within a defined age group, or to a

target population at known high risk, determined by ethnic group or genetic predisposition. Screening may sometimes be offered to a group exposed to a known causal factor, e.g. in the workplace, but there are no examples of this for prostate cancer.

#### AGE GROUPS

The optimum age range for screening is not known. Results from the two screening trials will provide information to make an informed decision; the ages covered in these screening trials are 45–80 years.

#### ETHNIC GROUPS

The high incidence and mortality from prostate cancer in African-American men (AAM) is well documented [2]. In addition, poor survival has also been reported, leading to suggestions that AAM may develop a more aggressive, faster growing form of the disease [31]. However, the reasons are likely to be multifactorial, and in part reflect differences in knowledge and awareness of the disease, and availability and use of healthcare. Some studies published from 2000 onwards suggested that past differences in stage and survival between black and white men in the USA may be disappearing with increased PSA testing. A study of 477 men attending an equal-access clinic in Los Angeles found no large differences in clinical stage or Gleason score between white and black patients [32]. However, the median total PSA level at the time of diagnosis was significantly higher in AAM (14.2 ng/mL) than in white men (9.4 ng/mL). An autopsy study [33] showed no difference between AAM and white men in the time of initiating prostate cancer but, with increasing age, high-grade prostatic intra-epithelial neoplasia and clinically significant prostate cancer were more prevalent among AAM than white men.

Underlying hormonal or biochemical differences may contribute to differences in the risk of developing prostate cancer among ethnic groups. A review of studies reporting racial differences in the androgen and androgen-receptor pathway in prostate cancer [34] confirmed that black men have higher circulating testosterone levels from birth to  $\approx 35$  years old than have white men, and that androgen-receptor mutations differed between Japanese and white populations. Differences in androgen receptor gene polymorphisms could explain racial

differences within the androgen/androgen receptor pathway.

#### HIGH-RISK FAMILIES

A family history of having an affected first-degree relative doubles the risk of developing prostate cancer. Targeted screening of male first-degree relatives of men diagnosed with prostate cancer when aged  $<65$  years should be evaluated. Carriers of *BRCA2*, found in 2–5% of men with early-onset prostate cancer, are at particularly high risk of developing prostate cancer [35,36]. The relative risk of developing prostate cancer by age 56 years from a deleterious germline *BRCA2* mutation was 23-fold [35].

Results of offering screening to men with a family history are mostly descriptive, and no studies appear to have evaluated the effect of screening on prostate cancer mortality. For example, a study in France [37] showed that the proportion of men with a family history who had a raised PSA level was higher than that in similar age groups in the general population, and was higher in families with an age of onset of prostate cancer of  $<65$  years than in families with a later age of onset.

#### CHOICE OF SCREENING TEST

PSA is a glycoprotein which is produced almost exclusively by the epithelium of the prostate gland. The level of serum PSA may be increased in several prostatic diseases, including benign prostatic hyperplasia (BPH) and adenocarcinoma. PSA levels may be greater in the latter because of increased production of PSA and architectural distortions in the gland that allow PSA to be more readily circulated. PSA may also be raised transiently after ejaculation or medical procedures such as biopsy and a digital rectal examination (DRE) [38].

Assays for measuring the concentration of PSA in serum are marketed by several manufacturers. As there is some variation in the calibration among the different assay kits, and other factors may cause variation in measurement between laboratories, an external quality-assurance scheme (NEQAS) [39] monitors this variation.

#### PERFORMANCE OF THE SCREENING TEST

The four main measures of performance are defined in terms of screening test results in a

**TABLE 2** Effects of strategies for PSA testing on screening sensitivity and specificity compared with using a total PSA of >4 ng/mL

Approach	Effect on	
	sensitivity	specificity
Threshold decreased from 4 to 3 ng/mL	Increased	Decreased
Use of age-related reference ranges	Slightly increased	Decreased
Total PSA, and when 4–10 ng/mL, free PSA and free/total ratio	Decreased	Increased
Total PSA and when 2.5–4 ng/mL, free PSA and free/total ratio	Increased	Decreased (more false-positives for a total PSA of 2.5–4 ng/mL)

(hypothetical) population for which the presence or absence of cancer is truly known. A positive test result does not mean that a person is absolutely certain to have cancer; nor does a negative test result mean that a person definitely does not have cancer. It is important to be able to convey the implications of positive and negative test results to those who are screened. The ability of the screening test to predict whether a person truly has cancer or not is measured by the positive and negative predictive values, respectively.

The performance of the screening test will also determine the proportion of cancers in the population that are detected (sensitivity), and conversely the proportion of people who do not have the disease who have a negative test (specificity). Ideally, both sensitivity and specificity should be high, but for most screening tests there is a compromise between them; the higher the specificity the smaller the proportion of false-positive results, and the lower the workload resulting from unnecessary referrals.

The performance of the test used to screen the general population will in part be affected by the threshold levels used to decide on referral for further diagnostic tests, and in part on the accuracy of the subsequent diagnostic tests. Ideally, the values of sensitivity and specificity should be estimated from screening trials where there are data from a long-term follow-up, including interval cancers. The effects of using different thresholds for PSA on the sensitivity and specificity of the test are summarized in Table 2.

In a cohort of men in Finland, sensitivities and specificities were 100% and 91%, respectively,

with a PSA threshold of 2.5 ng/mL, and 44% and 94%, respectively, with a threshold of 4 ng/mL [40]. Importantly, sensitivity and specificity improved more in men aged <65 years, a likely age for screening, than in older men. Other measures of PSA may improve the specificity of the test. In the USA, a modelling exercise, used to estimate sensitivity, provided disappointingly low values after adjusting for verification bias, which occurs when not all people have their disease status confirmed by biopsy [41]. However, this study started with a very low estimate of sensitivity before making the adjustment. In high-risk populations, age-related thresholds are required if screening starts when younger than in general population screening trials (e.g. <50 years).

The accuracy of the PSA value recorded for an individual patient is affected by individual factors (e.g. sexual activity, and a DRE before testing), laboratory standards and choice of assay [38,39]. Some have suggested that the PSA test should be repeated before deciding to refer based on certain thresholds [42]. The acceptability and cost of repeat tests need to be evaluated.

Other measures which might be used to detect prostate cancer are being investigated. For example, complexed PSA is reported to improve specificity [43], increased expression of human glandular kallikrein-2 has been reported in prostate cancer cells, and new assays for this factor may increase the specificity of cancer detection [44].

#### CHOICE OF SCREENING INTERVAL

The frequency of screening, i.e. the interval between screening rounds, is undecided for prostate cancer; in trials the interval was

1–4 years. Results from the RCTs [45] will inform an assessment of cost-effectiveness. In the Rotterdam arm of the ERSPC the sensitivity of the screening protocol involving PSA testing, DRE and TRUS was assessed using a count of interval cancers between screening rounds [46]. With a 4-year interval, the sensitivity was estimated to be 79.8–85.5%. The sensitivity will vary according to the type of test and threshold used for the PSA test.

#### FURTHER DIAGNOSTIC TESTS

After a positive screening test result, men are usually referred for further diagnostic tests. Most men will have a TRUS-guided prostatic biopsy, as ideally a histological diagnosis is required to confirm whether cancer is present or not. The biopsy also provides information on the volume and grade of the cancer, which are used with other information to determine the choice of treatment. The procedure for taking the biopsies will affect the detection rate of cancer. The number of cores taken can vary from six to 12 or more; there is some evidence that the number of cores is positively correlated with the detection rate of cancer, and the proportion of small cancers detected [47]. However, there is increasing evidence that selected sampling of certain areas of the prostate, notably the peripheral zone, without increasing the number of cores, will increase the detection rate of cancer [48,49].

There is variable reproducibility in the grading of prostate cancer [50,51]. Factors which help to improve the accuracy of grading include the level of expertise of the pathologist and use of a secondary review [52,53]. Moreover, among patients who undergo radical prostatectomy, the proportion of cancers found after surgery to be have been under- or over-graded at biopsy was 48% and 14%, respectively [52].

#### EFFECTS OF SCREENING ON DETECTION AND MORTALITY RATES

There are three main methods for studying the effects of screening on detection and mortality rates, i.e. ecological and observational studies, and the reference standard, RCTs. Effective screening will lead to an increase in the detection rate of early-stage cancer, which should be followed in turn by a decrease in the incidence rate of late-stage cancers and subsequently deaths

TABLE 3 Summary of observational studies published since 1 January 2000

	[60]	[61]	[62]
Place	Seattle-Puget Sound, USA	Quebec, Canada	USA
Period	1987–97	Incidence 1989–93 Mortality 1995–99	1988–95
Age range, years	65–79 in 1987	≥50	≥50
Prostate cancer outcome measures	Mortality	Incidence and mortality	Mortality
Rate of PSA testing	2.2 per 100 person years in Connecticut, 11.8 per 100 person years in Seattle	Not known	Not known
Results	No significant difference in prostate cancer rate ratio between cohorts	Incidence increased and subsequent mortality decreased in each cohort, but size of increase in incidence unrelated to size of decrease in mortality	Mortality increased, then decreased after 1992

from the disease. This is likely to be seen over a period of several years after one or more screening rounds.

#### ECOLOGICAL STUDIES

These studies involve comparisons of mortality and incidence rates using aggregated data which are compared with the rate of PSA testing. Such studies may be temporal or geographical [54]. The main limitation is that individual data are not available, so within the grouped data it is not possible to study the relation between reduction in mortality and whether an individual has been screened or not. Thus other factors such as increased awareness in the population and improvements in treatment, all of which may be stimulated by increased screening, cannot be separated from the effect of screening.

Since 2000, results have been published on temporal changes in several countries, including France [55] and Canada [3]. Trends in incidence by age, and sometimes stage, and in survival and mortality have been studied in relation to the introduction of PSA testing. The lack of individual-based data and of accurate data on the proportion of men tested makes the interpretation of these results very difficult.

Geographical differences were studied in Austria [56,57] (1993–9, age range 45–75 years), and Canada [58] (1985–99, age range 50–74 years). The results of a geographical comparison of prostate cancer mortality in Tyrol, Austria (PSA testing encouraged and available with no charge from 1993), with the rest of Austria (where the test was not introduced) are emerging

[57]. At least two-thirds of men in Tyrol had at least one test in the first 5 years of the study. Although the mortality rate for prostate cancer reduced in the rest of Austria, the decline was most marked in Tyrol. The reduction in mortality occurred earlier than would be expected by screening alone. The authors suggest that PSA screening may lead to a marked reduction in prostate cancer mortality over 5 years of follow-up when a marked decrease in the distribution of stage at diagnosis is accompanied by high-quality urology and radiotherapy treatment [59]. In British Columbia, Canada [58], trends in incidence and mortality were compared among 88 areas classified by the intensity of PSA screening. There appeared to be no association between a decrease in mortality from prostate cancer and different intensities of PSA testing. The quality and completeness of data on PSA testing will affect the results of these studies.

#### OBSERVATIONAL STUDIES

Two cohorts of men were studied in Seattle-Puget Sound where there had been intensive screening and treatment for prostate cancer, and in Connecticut where there had been low levels of screening and radical treatment [60] (Table 3).

Although the rates of PSA testing and radical prostatectomies were more than five times higher in Seattle than in Connecticut, there was no difference in the adjusted rate ratio of prostate cancer mortality up to 1997. Limitations with the study included the comparison of only two areas, the age of men being ≥65 years in 1987, which is higher than that of men most likely to be offered screening, a follow-up only up to 11 years,

and incompleteness of data, which may have caused an underestimate of the rate of PSA testing.

In Quebec, Canada [61], the change in incidence and mortality at age ≥50 years was studied in birth cohorts. Although most cohorts showed an increase in prostate cancer incidence in successive cohorts and a subsequent decrease in mortality, there was no inverse relation between the measures. This reinforces the suggestion that the type of treatment may be a major contributor to changes in mortality.

The incidence-based mortality method involves studying mortality which is linked to individual men diagnosed with prostate cancer in specific periods. Thus other data such as stage and grade at time of diagnosis can be linked to mortality. Using the SEER data [62], there was an increase and then decrease after 1992 in mortality rates in different groups defined by age, ethnic group and grade.

#### RCTs

No RCT has yet reported on the effects of screening on mortality from prostate cancer. Trials are in progress in Europe and in the USA [63,64], both designed to have adequate statistical power to analyse mortality after 10 years of follow-up (Tables 4 and 5) [65]

The trial in Europe (ERSPC) [64] as reported in 2001 has seven centres currently participating (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden and Switzerland). The intended number of men recruited is 182 600; the overall age range is 50–74 years, with the core age group being 55–69 years

TABLE 4 Summary of the screening programmes in the European and North American trials in 1996 [65]

Item	Belgium	Canada nationwide	Canada, Quebec	Finland	Italy	Rotterdam NL	Nijmegen NL	Sweden	USA
Endpoints									
Death from prostate cancer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type of trial	PB	Efficacy	PB	PB	PB	PB	PB	PB	Efficacy
Randomization	AC	AC	AC	BC	AC	AC	AC	BC	AC
Period	1991–98	1996–2000	1988–	1996–99	Not defined	1992–98	1996–99	1995–96	1993–97
Age at entry, years	55–74	55–74	45–80	55–67	50–69	55–74	55–70	50–65	(55–) 60–74
Target sample									37 000
Screening group	8750	36 000	8032*	22 500	27 500	20 000	10 000	16 200	37 000
Control group	8750	36 000	20 000	45 000	27 500	20 000	10 000	16 200	37 000
Screening test†									
PSA, ng/mL	4.0	4.0	3.0	2.0/4.0	4.0	4.0	4.0	3.0	4.0
DRE	All	PSA > 2.0	All	PSA driven	All	All	PSA driven	No	All
TRUS	All	No	PSA > 3.0 and/or DRE positive	No	No	All	PSA driven	No	No
Screening interval, years	4	2	1	4	4	4	4	2	1

PB, population-based; AC, after consent; BC, before consent; \*Number of men enrolled to date; †The threshold level for PSA, criteria for application of other screening test.

TABLE 5 Summary of results from the European trial [63]

Centre	Randomization, N		Total, C	N screened (% of A)	Cancer in A N (% of C)*	Cancer in B N (%)†
	Screen (A)	Control (B)				
Belgium‡	4 666	4 618	9 276	4 103 (87.9)	96 (2.3)	93 (2.0)¶
Finland	32 000	48 458	80 458	21 980 (67.6)	634 (2.9)	312 (0.64)
France (ongoing)	1 054	1 024	2 078	380 (36.1)	12 (3.2)	–
Italy	7 518	7 495	15 013	5 368 (71.4)	87 (1.6)	20 (0.27)
Netherlands	21 210	21 116	42 376	19 970 (94.1)	1014 (5.1)	265 (1.3)
Spain	2 416	1 862	4 278	2 416 (100.0)	40 (2.3)	7 (0.4)
Sweden	9 972	9 973	19 945	6 982 (70.0)	205 (2.8)	192 (1.9)
Switzerland (ongoing)	4 809	4 805	7 457	4 316 (89.7)	139 (3.2)	2 (–)
Total	83 645	99 393	183 038	65 515 (78.3)	2227 (3.4)	891 (0.90)

\*Detection rates; †data incomplete, registry delays; ‡re-screening after 7 years; ¶probably because of long interval.

old [64]. The central aim of the ERSPC trial is to compare prostate cancer mortality in men randomized to be offered screening with that in a control group. There are differences in protocol among the centres; some of these concern methods of recruitment (general population with randomization before consent, or a selected population who have given consent), the number of screening methods offered (some centres do or have in the past included a DRE and TRUS with PSA testing), the interval between routine re-

screens and the criteria for recommending biopsy (although adopting a PSA threshold of  $\geq 4$  ng/mL has led to this in all centres at all times). In the first round of screening, the detection rates of prostate cancer were 11–42 per 1000 men [64]. The range will in part reflect differences in underlying incidence rates among countries, but also the use of different screening procedures.

The Prostate, Lung, Colon and Ovary (PLCO) trial [64,66] in the USA aims to recruit 74 000

men aged 55–74 years and randomized to two equal groups. Those in the intervention arm will be offered four annual screens by PSA and a DRE. In the pilot study, which included  $\approx 10 000$  men, methods of recruitment led to a selected population, with a large percentage of men in the control arm having had a recent PSA test, and recruitment methods have now been altered to attempt to recruit a more suitable population. The ERSPC and PLCO have agreed to co-ordinate their work to facilitate combined (overview) analysis [67].

A trial in Quebec reported a reduction in prostate cancer mortality of 69% in screened men [68]. Unfortunately, the results are at present uninterpretable [69] because of the low compliance rate (23%) and invalid analytical procedures aimed at overcoming this. Further details of the study, including the outcome of screening by the PSA test and DRE in the prevalent and subsequent rounds of screening, were reported [70]. However, the fundamental limitations associated with the low uptake rate of screening will lead to various biases in the results.

The ability of these trials to detect a difference in the mortality rates between men offered screening and men in the control arms will depend in part on the level of contamination from ad hoc screening. In the reports on mortality there is the potential bias from misclassification of cause of death [71].

#### TREATMENT OF EARLY-STAGE PROSTATE CANCER

The outcome of treatment will affect the overall advantages and disadvantages of screening. Some men will be over-diagnosed and will receive unnecessary treatment. Certain treatments will have side-effects that will lead to various degrees of symptoms or even death.

Few RCTs of early-stage prostate cancer have been completed. One study from Sweden [72], compared the outcome of watchful waiting with radical prostatectomy in 695 men newly diagnosed from October 1989 to February 1999 with prostate cancer of TNM clinical stage T1b, T1c, or T2, and a median of 6.2 years of follow-up. Radical prostatectomy significantly reduced the disease-specific mortality by  $\approx 7\%$ , and reduced the rate of development of distant metastases by 14% after 8 years. With a longer follow-up there is the potential for a greater reduction in disease-specific mortality. However, there was no significant difference between surgery and watchful waiting in terms of overall survival. Also, with the development of active management, which offers monitoring of the disease until it shows signs of significant growth, the rate of development of distant metastases and disease-specific death may be lower than that associated with watchful waiting. In addition the cases included in this trial will differ from men with screened-detected cancers, for whom the lead time in

diagnosis is probably  $>5$  years, and in whom the proportion of slow-growing cancers will be higher.

Other RCTs are underway; the ProtecT study in the UK [73] is randomizing men whose cancer was detected after an invited PSA test to undergo radical prostatectomy, radical radiotherapy or active management. In the treatment arm of the study, cases are identified by offering PSA testing in men registered in the study general practices. A control arm has now been added to ProtecT, so that the effects of PSA testing for case-finding can be compared with routine diagnosis and care. The PIVOT trial in the USA [74] is now closed, with 731 patients randomized to radical prostatectomy or watchful waiting, and half of the participants have impalpable disease.

The side-effects of treatment and the resulting quality of life are significant factors when considering options for treatment. Nerve-sparing radical prostatectomy carried out by experienced surgeons at high-volume centres can lead to only 10–25% of men having severe incontinence, and a few becoming impotent [75]. Death after surgery is very unlikely, but these rates vary according to the experience of the surgeon and health of the patient at the time of surgery. Radical radiotherapy is associated overall with higher levels of incontinence and some complications with the bowel. With the introduction of new techniques such as conformal radiotherapy [76], the rate of complications will be reduced. Complications associated with watchful waiting should not be overlooked. If the cancer progresses, and changes are not detected early, problems with erectile dysfunction and urinary leakage, as well as later complications associated with the development of metastases, can be significant [77].

Biological markers to help identify cancers when they are likely to become aggressive, and new technologies to improve the staging of cancer, will help to optimize the choice of patient management [78]. Active surveillance would aim to individualize therapy by selecting only those patients who have significant cancer for curative therapy by radical prostatectomy or radiotherapy. Patients would be closely monitored and a decision to treat radically would be based on evidence of disease progression. This approach could offer significant benefits in

terms of quality of life, if progression can be accurately monitored so that there is a low risk of developing metastases.

#### AD HOC SCREENING

##### IN THE UK

Despite the lack of evidence for the effectiveness of screening in reducing mortality from prostate cancer, increased testing for PSA has certainly contributed to the rising incidence of prostate cancer in the UK (Table 6). Using data from the IMS MediPlus database to report on the annual proportion of men receiving the PSA test in general practice, in 1994 [79], 12 109 of 150 353 men (1.4%) aged  $\geq 45$  years in 1994, with no previous history of prostate cancer, had a PSA test noted on their record that year. By 1999, the proportion was 3.5% [80]. However, the increase may in part reflect improvements in the recording of PSA tests in GPs' notes, as well as increased testing, and it was not possible to distinguish between screening and diagnostic testing. A study in general practices associated with one hospital in Wales found that during one month, 24% of PSA requests were for screening purposes, but it is unclear how complete these data were [81]. In contrast, the proportion of PSA requests associated with screening was much lower (3.2%) in a study of seven centres in the south-west of England [82].

A study was conducted to investigate the rate of PSA testing in general practice with specific reference to testing in asymptomatic men in England and Wales. Data were collected during a 6-month period from 1 December 2001 from 391 practices which had a total of 469 159 men aged 45–84 years registered. It was estimated that 1.6 asymptomatic tests per 100 men would have been conducted in one year, and a total of 5.4 tests per 100 men would have been conducted in men with no previous diagnosis of prostate cancer. Adjustments were made for missing values and the social deprivation score, as the study sample under-represented single-handed and inner-city practices.

There are no readily available population-based data with which to study the rate of private PSA testing in the UK. In the study by Melia *et al.* (personal communication, 2003), it was shown that there was a higher proportion of men aged  $<65$  years being tested privately

TABLE 6 Summary of reports on rates of PSA testing

Place	Year	Rate of testing
UK [79,80]		In men aged > 45 years tested in general practice, where there was no previous diagnosis of prostate cancer
	1994	1.4% men tested per annum
	1999	3.5% men tested per annum
England and Wales [83]	2001–2002	In men aged 45–84 years tested in general practice pa, where there was no previous diagnosis of prostate cancer: 5.4 tests per 100 men per annum
Northern Ireland [84]	1993–99	30% of men aged ≥ 50 years at least one PSA test either in general practice or at hospital.
	After 1995	6% men aged ≥ 50 years estimated to have a PSA test pa
USA	1992	In Minnesota [85]: >40% of men aged ≥ 60 had had at least one test in their lifetime
	1994–97	In a telephone survey [86]: rate increased from 33% to 54% in men aged ≥ 50 years
	1995–96	In visits to USA primary-care physicians [87]: 7% of men aged 60–79 years had test
	1998	In Medicare records [88]: 38% of black men and 31% of white men aged ≥ 65 years had a test
Australia:		
South [89]	1995	25% aged ≥ 40 and no previous prostate cancer had had at least one test
South [90]	1996	20% aged ≥ 40 had had a test in the previous year
New South Wales [91]	1995–96	27% aged > 50 years had had at least one test
Sydney [92]	1999	23% aged 40–70 years consulting their GP for any condition reported having had a PSA test
Spain [93]	1997–99	21.6 per 1000 person years
Milan, Italy [94]	1999–2000	26.9% in men aged ≥ 40 years
Florence, Italy [95]	2000	12–16% in men aged ≥ 50 years tested at least once in one year
Rotterdam [96]	1997–2000	Defined by PSA ≥ 3 ng/mL followed by biopsy, in 2.9 years, general population rate 33 per 1000 person years, control arm of screening study 20% or 73 per 1000 person years
Norway [97]	1999	7% aged 50–65 years; not population-based

than by GPs, and that the levels of PSA by age were relatively lower in the private data than in the GP data.

#### WORLDWIDE

There is considerable variation in the extent of testing among countries (Table 6) [83–97] but because there are no routine, standardized data, it is difficult to compare results among studies and thus countries. The highest proportion of the male population being tested for PSA is in the USA, which is reflected in the very high incidence rates reported there compared with other countries.

#### CONCLUSIONS AND IMPLICATIONS OF SCREENING

The present state of knowledge about the value and outcome of screening for prostate cancer can be summarized in relation to the criteria for screening as:

- Is the disease a major health problem? Yes.
- Is the natural history of the disease known? No.

- Is there an efficient screening test? No, not as efficient as mammography.
- Is the test free of complications? Yes.
- Is there an agreed effective mode of treatment? No.
- What is the quality of life associated with screening? Depends on acceptability and level of side effects from treatment, but potentially poor.
- Does screening reduce prostate cancer mortality? Not known.
- Is screening cost-effective? Not known.

The use of the serum PSA assay continues to increase, despite there being no conclusive evidence of the efficacy and effectiveness of screening to reduce mortality from prostate cancer.

Results from the ProtecT study of men aged 50–60 years in England and Scotland show that the uptake rate of case finding was 50% (this may be affected in that the men are then randomized into a treatment trial), the proportion of men with PSA levels of ≥3.0 ng/mL was 10%, and the cancer detection rate in men screened was 2.5% (Donovan, personal communication, 2004). Using this

information, in the prevalence round of screening a sample of 1 million men aged 50–60 years, 100 000 men would have a raised PSA level, and 2500 men would be diagnosed with prostate cancer.

At present in England, there are >5 million men aged 50–60 years and there are 1586 prostate cancers diagnosed annually in this age group. Even with an uptake rate of, e.g. 50%, a national screening programme has the potential to cause a huge increase in the number of men referred for biopsies, and the number cancers detected.

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Abbreviations: **RCT**, randomized controlled trial; **SEER**, Surveillance Epidemiology and End Results; **TCR**, Thames Cancer Registry; **AAM**, African-American men; **ERSPC**, European Randomized Study of Screening for Prostate Cancer; **PLCO**, Prostate, Lung, Colon and Ovary (trial).

## APPENDIX 1

Literature search strategies:

*Screening Report*

Main data source: PubMed

Main time period: January 2000 to February 2004

Main search terms:

prostatic neoplasms AND (natural history OR prognosis) NOT (protein OR ablation OR phase II OR prostatectomy OR radiotherapy OR androgen deprivation OR hormone OR antiandrogen OR castration)

mass screening AND prostatic neoplasms prostatic neoplasms AND cohort studies NOT (radiotherapy OR prostatectomy OR chemotherapy OR antiandrogen OR androgen)

prostatic neoplasms AND diagnosis AND prostate specific antigen AND (sensitivity and specificity)

prostatic neoplasms AND diagnosis AND prostate specific antigen AND (sensitivity OR specificity)

prostatic neoplasms AND (mortality OR morbidity) AND rate NOT (phase II OR phase III OR trial OR androgen OR radiotherapy OR chemotherapy OR suramin)

clinically significant AND prostate cancer AND (screening OR early detection OR PSA) NOT (treatment OR prostatectomy OR radiotherapy)

Over 3000 references were identified. Using the titles and abstracts, papers were selected for further assessment. Each paper included

in the review was then entered in to the Reference Manager database, a copy of the paper was obtained, and a one-page cover sheet summarizing the content of the paper and its limitations was completed. The content of the summary sheet was entered into an ACCESS database.

Additional references were identified when reading the articles found in this search. Given the breadth of the search it was not feasible in the time funded to conduct a systematic search and review of all topics over a wider period.

## APPENDIX 2

Criteria for assessing the benefits and disadvantages of screening (<http://www.nsc.nhs.uk/>).

- The condition should be an important health problem; (i) the epidemiology of the condition should be known; (ii) the natural history of the condition should be understood; (iii) there should be a recognized latent period or early symptomatic stage.
- All cost-effective primary prevention interventions should have been implemented as far as practicable.
- There should be a simple, safe, precise and validated screening test.
- The distribution of test values in the target population should be known, and a suitable threshold defined and agreed.
- The test should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals.
- There should be an effective treatment or intervention for patients identified through early detection.
- There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
- Clinical management of the condition and patient outcomes should be optimized by all healthcare providers before participating in a screening programme.
- There should be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity.
- There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable to health professionals and the public.
- The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
- The opportunity cost of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole.
- There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
- Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available before starting the screening programme.
- All other options for managing the condition should have been considered (e.g. improving treatment, providing other services).