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Preface

The purpose of this booklet is to provide the primary care team with an easy reference to assist them in providing men with information on the benefits and limitations of the PSA test for prostate cancer.

Development of this booklet was informed by consultation with over 100 GPs and Primary Care Cancer Leads, as well as advice from an expert, multi-disciplinary group set up by the Department of Health to advise on all aspects of the Prostate Cancer Risk Management Programme. Membership of this expert group is listed below.

The authors accept responsibility for the final text of these materials.

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Contents

1 Introduction

Prostate cancer is now the second most common cause of cancer deaths in men (1). Recently there has been considerable media focus on the disease, along with calls for the introduction of a national prostate cancer screening programme. PSA testing can lead to the diagnosis of localised prostate cancer when potentially curative treatment can be offered. However, there are a number of uncertainties surrounding the PSA test and the diagnosis and treatment of prostate cancer. Currently there is no good evidence that the benefits of a screening programme would outweigh the harms.

Albert Mulley, Chief of General Medicine at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School, summarised the issues in 2002:

"As a 54 year old man, it is important that I understand that PSA testing makes it more likely that I will learn that I have prostate cancer - and that I will learn so sooner rather than later. Without testing I face about a 10% chance of having prostate cancer diagnosed in the remainder of my lifetime, and less than a 4% chance of dying because of it.

Based on what has happened to prostate cancer incidence as PSA screening has spread in the United States, I believe a decision to be screened would increase my chance of being diagnosed to approximately 20%, and the diagnosis would come 5 to 8 years earlier.

There is no good evidence that the greater likelihood of knowing, and knowing sooner would reduce my chances of a prostate cancer death."

The Prostate Cancer Risk Management Programme and informed choice.

In response to growing public concern about the risks of prostate cancer the government has launched a Prostate Cancer Risk Management Programme (2;3). One of the main aims of the programme is to ensure that men who are concerned about the risk of prostate cancer receive clear and balanced information about the advantages and disadvantages of the PSA test and treatments for prostate cancer. It is hoped that this will enable men to make more informed decisions about PSA testing. This is considered to be very important because the data regarding the effectiveness of PSA testing are unclear and patients face potentially serious consequences to their health in either accepting or declining the test. Furthermore, many men have inaccurate or incomplete knowledge about the PSA test gained either from the media or through friends and relatives. The patient's personal preferences should be an important factor in the decision as fear of cancer, the potential impact of treatment complications on quality of life and the importance of the current lack of hard scientific proof will vary between men (4).

This booklet provides background information about the diagnosis and treatment of prostate cancer and outlines the issues surrounding the use of the PSA test. The booklet is part of an information pack which also contains a summary card and patient information sheets (5).

The Prostate Cancer Risk Management Programme aims to help the primary care team give clear and balanced information to men who **ask** about testing for prostate cancer.

2 Prostate cancer background information

2.1 Incidence and mortality

Prostate cancer is the second most common cause of cancer-related deaths in men in the UK. Each year over 20,000 men are diagnosed with prostate cancer and 9,500 die from the disease (1).

Prostate cancer is largely a disease of older men and is rare below the age of 50 (see figure 1). The median age of both diagnosis and mortality is 75 years. The numbers of deaths by age in 1999 are shown in figure 2. Over 90% of prostate cancer deaths occur in the 65 and over age group. By the age of 80 about 60-70% of men will have some cancer cells in their prostate. However only around 1 in 30 of these men will die **of** their prostate cancer (6).

The number of prostate cancer cases has risen steadily over the last two decades (1). Part of the increase is a result of ageing of the population. However, improved ascertainment by cancer registries, improved diagnostic accuracy and additional methods of disclosing prostate cancer have also contributed to the increase in age specific incidence. Initially this came from the use of trans-urethral resection of the prostate (TURP) as therapy for benign disease, with mandatory histological examination of chips removed during TURP. Subsequently there has been a widespread increase in the use of the prostate specific antigen (PSA) test. These tests have led to the diagnosis of many cancers, some of which would not have presented clinically within the man's lifetime (7).

Men are more likely to die **with** prostate cancer than **of** it.

Figure 1
Number of new cases of prostate cancer by age in the UK, 1997

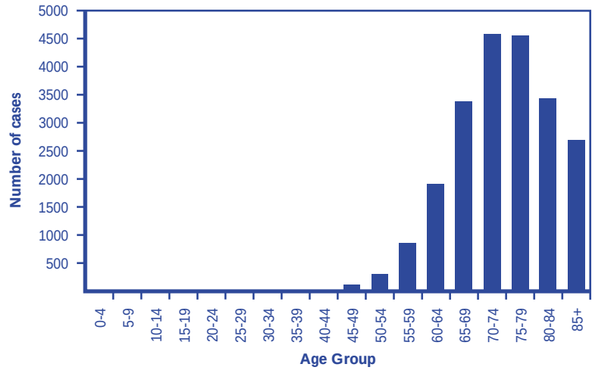
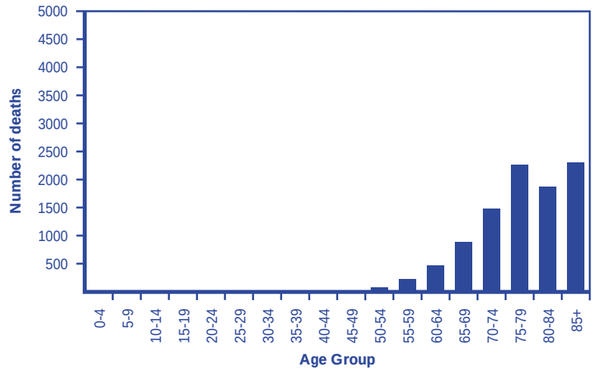


Figure 2
Number of deaths from prostate cancer by age in the UK, 1999



2.2 Natural history of prostate cancer

The natural history of prostate cancer is not fully understood. Prostate cancer is not a single disease entity but more a spectrum of diseases ranging from very aggressive to slow growing tumours, which may not cause any symptoms or shorten life. Many men with less aggressive disease tend to die **with** rather than **of** their cancer, but it is not always possible to tell at diagnosis which tumours are aggressive and which are slow growing.

2.3 Risk factors for prostate cancer

The causes of prostate cancer are not known, although hormonal influences have a role to play in the development of the disease since tumours regress with androgen deprivation.

The strongest risk factor is age, but the following also play a part:

Family History
Prostate cancer often clusters in families and approximately 5-10% of cases are thought to have a substantial inherited component (8). It has been estimated that a strong predisposing gene could be responsible for 43% of cases by age 55 (9). Research is underway to identify prostate cancer predisposition genes (10).

The relative risk of prostate cancer is increased 2-fold with one first degree relative diagnosed aged 70 or under and rises to 4-fold with 2 relatives, if one of them is diagnosed under the age of 65. The risk with three or more relatives affected is increased 7-10 fold.

At present, there are no definitive guidelines for prostate cancer screening in high risk families in the UK. You may want to contact your local genetics centre for further advice if your patient has a significant family history.

Ethnicity
The incidence of prostate cancer is higher in African Americans (about twice that in white men), and lowest in Asian and Oriental men (11).

Diet
A diet high in animal fats and proteins may increase the risk of developing prostate cancer (12).

There is often increased anxiety amongst men with risk factors. If these men present in primary care it is important they receive the best available information and support to assist them in deciding whether or not to have a PSA test.

However, until more evidence is available about screening for prostate cancer, active case finding of men with risk factors is not recommended.

2.4 Clinical features

2.4.1 Localised prostate cancer

Localised prostate cancer (confined within the capsule) is usually asymptomatic. Prostate cancers, unlike benign prostatic hyperplasia, tend to develop in the outer part of the prostate gland. It is unusual for these early cancers to cause any symptoms. Tumours have to be quite large to cause a pressure effect on the bladder or urethra, by which time they have usually metastasised. Localised cancers range from just a few cells to more extensive disease which is considered 'clinically important'.

2.4.2 Locally advanced prostate cancer

These cancers have extended outside the prostatic capsule and are also frequently asymptomatic.

2.4.3 Metastatic prostate cancer

Often the first sign of prostate cancer is evidence of metastases. Prostate cancers frequently metastasise to the bones, causing pain. Appearance on x-ray is usually as a non-lytic lesion.

About 20-30% of patients in the UK present with metastatic disease (7;13).

2.5 Lower urinary tract symptoms (LUTS) and prostate cancer

Lower urinary tract symptoms (LUTS) are common in older men. It is important to realise that early prostate cancer itself usually will not produce symptoms and that LUTS (frequency, urgency, hesitancy, terminal dribbling) are usually the result of benign prostatic hyperplasia (BPH). 70-80% of prostate tumours originate in the peripheral zone of the gland distant from the urethra (14). As a consequence, by the time prostate cancer itself causes LUTS it will usually have reached an advanced and incurable stage.

Due to the high incidence of BPH and prostate cancer in the older age group, some men will have a benign pathology and a co-existing early prostate cancer (15). When a man seeks advice about LUTS this can set in train investigations which diagnose what is a coincidental prostate cancer.

There is no good evidence to suggest that the presence of LUTS is predictive of localised prostate cancer.

Experts disagree as to whether men with LUTS should 'opt-in' or 'opt-out' of the PSA test, but all agree about the importance of fully counselling these men about the test implications (16).

3 Detecting prostate cancers

There are a number of ways of detecting prostate cancers:

- The prostate specific antigen (PSA) test
- The digital rectal examination (DRE)
- The transrectal ultrasound guided (TRUS) prostate biopsy

3.1 The PSA test

The PSA test measures the amount of prostate specific antigen (PSA) in the blood. The PSA test is currently the best method of identifying localised prostate cancer. However, since PSA is an enzyme also found in men without prostate cancer, and PSA values tend to rise with age, the difficulty in using this marker comes in defining the 'normal' range and knowing when referral and biopsy are appropriate.

3.1.1 Test limitations

- The PSA test is not diagnostic: those with an elevated PSA will require a transrectal ultrasound guided (TRUS) prostate biopsy to obtain a tissue on which a diagnosis may be made.
- PSA is tissue specific but not tumour specific in the prostate (17). Therefore, other conditions such as benign enlargement of the prostate, prostatitis and lower urinary tract infections can also cause an elevated PSA. About ⅔ of men with an elevated PSA do NOT have prostate cancer detectable at biopsy (6).
- **Up to 20% of all men with clinically significant prostate cancer will have a normal PSA (18).**
- The PSA test will lead to the identification of prostate cancers which would not have become clinically evident in the man's life time.
- The PSA test will not, in itself, distinguish between aggressive tumours, which are at an early stage but will develop quickly, from those which are not aggressive.

All men should know they are having a PSA test and be informed of the implications prior to testing.

Opportunistic PSA testing is not recommended.

3.1.2 PSA test practicalities

Evidence indicates that PSA is stable in whole blood for up to 16 hours at room temperature. When taking blood you should ensure that the specimen will reach the laboratory and be separated within this time frame.

Samples should only be sent to laboratories which participate in the National External Quality Assessment Scheme (NEQAS).

Before having a PSA test men should NOT have:

- an active urinary infection
- ejaculated in the previous 48 hours
- exercised vigorously in the previous 48 hours
- or had a prostate biopsy in the previous 6 weeks.

If practical, do the PSA test before the DRE. If not, the recommendation is to delay the PSA test for one week after the DRE (19).

3.1.3 Referral guidance

The Prostate Cancer Risk Management Programme recognises that currently there is a wide range of practice around the country, with laboratories in some areas using a single cut-off value of 4 ng/mL and others providing age-related reference ranges. Further work is being done to consider the evidence in this area with the aim of standardising the test itself and the cut-off values used.

The Prostate Cancer Risk Management Programme, as interim guidance, recommends the following cut-off values are used for the PSA test (20;21).

Age (years)	PSA cut-off (ng/mL)
50-59	≥ 3.0
60-69	≥ 4.0
70 and over	> 5.0

Whereas a very high PSA reading is strongly suggestive of cancer, it is less clear when the PSA is mildly elevated.

3.2 Digital rectal examination of the prostate

The digital rectal examination (DRE) is a useful diagnostic test for men with lower urinary tract symptoms or symptoms suggestive of metastatic disease. It allows assessment of the prostate for signs of prostate cancer (a hard gland, often with palpable nodules) or benign enlargement (smooth, firm, enlarged gland).

Although cancer of the prostate may produce changes detected on a DRE these are not specific and many early prostate cancers will not be detected by DRE (22).

There is data to suggest that the addition of DRE to the measurement of PSA in the context of screening asymptomatic men adds little to the sensitivity (23).

DRE is a useful diagnostic test for men with symptoms.

DRE is not recommended as a screening test in asymptomatic men.

3.3 Transrectal ultrasound guided (TRUS) prostate biopsy

A TRUS biopsy involves taking 6-10 cores of prostatic tissue through the rectum under ultrasound guidance. Sometimes a lesion can be seen and biopsied under ultrasound guidance. However, often no lesion is seen and a series of biopsies are then taken in a systematic manner. If a tumour is detected histological examination reveals how well-differentiated the tumour is. Tumour differentiation is graded by a Gleason score: the lower the score the more well-differentiated the tumour, the less likely the tumour is to progress and the better the prognosis.

Men undergoing a TRUS biopsy should be aware of the limitations and complications of the test:

- Most men describe the biopsy as an uncomfortable experience and some describe it as painful.
- The biopsy procedure can cause significant anxiety.
- Up to 20% of tumours are not sampled (missed) at biopsy partly because some cancers appear homogenous with normal prostate tissue on ultrasound (false negatives) (24).
- Management of men with a negative biopsy but a persistently elevated PSA is very difficult. Prolonged periods of follow-up, with the possibility of re-biopsy may cause considerable anxiety.
- Complications:
  - Post-biopsy complications include bleeding and infection, with reported rates varying widely (6). A study from Holland reported that 0.4% men had to be admitted to a hospital following a biopsy (25).
  - Approximately ⅓ of men get some haematuria/haematospermia in the three months following the biopsy. All patients should receive prophylactic antibiotics to reduce the risk of infection. Reported rates of septic symptoms after prophylactic antibiotics range from minimal to over 1% (6;26)

Approximately two thirds of men undergoing TRUS biopsy because of an elevated PSA are not found to have cancer.

The best management for those with a persistently elevated PSA but negative biopsies is unclear. These men may face prolonged periods of follow up and experience considerable anxiety.

4 Treatments for prostate cancer

The management of localised prostate cancer is central to the controversy surrounding screening.

Men considering a PSA test should understand that:

- There is no strong evidence to show whether or not treatment of localised prostate cancer will lead to a reduction in mortality.
- There is no strong evidence to indicate which treatment option is most suitable for which man.
- Active treatments have significant side effects.

4.1 Treatment options for localised prostate cancer

There are three main treatment options:

- Active monitoring
- Radical prostatectomy
- Radiotherapy

There is continuing debate regarding the appropriate selection of patients for the different treatment options.

Comparisons of efficacy between treatment options are difficult because of differences in case mix, staging and treatment techniques. Randomised controlled trials such as the ProtecT Trial are underway. This is a large UK trial comparing radical prostatectomy, radical radiotherapy and active monitoring. The study is recruiting between 2001 and 2006 and the primary outcome is 10 year survival.

Complication rates are also hard to interpret for the reasons above, and also because of differences in the definitions of complications and whether short or long term complications are reported.

To date, there is no data from randomised controlled trials giving evidence about the **optimum treatment** for localised prostate cancer.

To date, there is also no data from randomised controlled trials to say whether or not any treatment option reduces **overall mortality** in men with localised prostate cancer.

4.1.1 Active monitoring

In active monitoring the patient is followed up regularly by a urologist. This approach is based on the premise that there are some men with prostate cancer who, on the grounds of their age or co-morbidity or on the basis of having slowly progressing tumours will die from other causes and will not suffer significant morbidity from their prostate cancer. A decision to offer radical treatment (surgery or radiotherapy) may be made on the basis of a rising PSA level or a change in the DRE.

This approach is non-invasive and avoids unpleasant side effects, but the downside is that some men will develop metastatic disease. Some men may find the uncertainty associated with this approach very difficult to cope with.

Active monitoring is often the treatment of choice for men with an estimated life expectancy of less than 10 years. However, it is also an option for men with greater life expectancies who wish to avoid the unpleasant side effects of surgery or radiotherapy and should be discussed with all men whose cancer is believed to be localised (13).

4.1.2 Radical (total) prostatectomy

The aim is to remove the entire prostate gland and to cure the disease. Complete tumour clearance is not always achieved. Up to 40% of patients who undergo surgery are found to have capsular penetrance or positive resection margins (27). Approximately half of these go on to develop biochemical or clinical recurrence of the disease. Recurrence does not, however, necessarily equate with either significant health problems or death from prostate cancer.

Complications of surgery include operative mortality, impotence and incontinence. Varying complication rates are reported in the literature. The mortality rate in all major reported series is now less than 1% (28).

Several factors have been shown to influence post-operative sexual function (e.g. age, clinical and pathological stage and surgical technique) Reported frequencies of impotence range from 20% to 80% (6;29).

Incontinence is a significant problem for many patients after radical prostatectomy. It is difficult to quantify and there are wide variations in the definitions and assessment of incontinence between studies. Reported incidences of incontinence range from 4-21% for mild or stress incontinence and from 0% to 7% for total incontinence 18 months post-operatively (6).

This treatment is not usually recommended for men with less than 10 years life expectancy.

4.1.3 Radiotherapy

Radiotherapy aims to cure the disease. As for prostatectomy, reported complication rates vary widely and are difficult to interpret.

Short-term side effects relate mainly to bowel and bladder problems from the radiation.

Longer term complications include impotence and urinary problems. Reports of impotence range from 25-60% (6;29), and reports of incontinence range up to 5% (6;29). Approximately 10% of patients have diarrhoea/bowel problems requiring treatment and up to 30% have occasional episodes of rectal bleeding.

This treatment is not usually recommended for men with less than 10 years life expectancy.

4.1.4 Brachytherapy

Brachytherapy involves the insertion of radioactive seeds into the prostate. It is currently only available in a few centres in the UK and the effectiveness of this treatment is not yet known.

4.1.5 Adjuvant therapy

Adjuvant hormone therapy is being increasingly used in conjunction with radiotherapy for apparently localised disease or after surgery in those with positive resection margins or poor prognostic factors (28).

Hormone therapies (LHRH analogues or anti-androgens) attempt to suppress growth of the cancer by reducing circulating androgen levels. They can be used as adjuvant treatments to those outlined above and are also widely used in the control of metastatic disease.

Side effects include impotence, loss of libido, breast swelling and hot flushes.

4.2 Locally advanced and metastatic prostate cancer

Clinically advanced localised cancer cannot be eradicated by surgery alone. The rate of progression of the disease varies considerably. Patients with locally advanced disease mainly receive radiotherapy or hormone therapy. Some men live for many years with few symptoms, whilst others develop extensive disease quite rapidly.

4.3 Monitoring effectiveness of treatment with PSA

PSA levels are used to monitor disease activity in those with established prostate cancer, giving an indication of response to treatments. It can also give an early indication of the progression of a cancer.

5 Population screening for prostate cancer

There have been calls for a national screening programme for prostate cancer, just as there are for breast and cervical cancers. This is a highly controversial area with much written on the topic (see for example 4;31;32). Recent falls in the mortality rates in the USA (where there is widespread PSA testing) are often cited as being indicative of an effective screening test (33). However, randomised controlled trials are needed to get a true assessment of the impact of screening. Two trials are currently underway in the United States and Europe (34). Definitive information from these trials will not be available until later this decade. A trial from Canada has already reported some data (35) but the findings are very controversial.

The Tyrol study in Austria has recently compared prostate cancer mortality in the Tyrol where PSA testing is freely available with the rest of Austria (where it is not) and shown significantly reduced mortality in the Tyrol (36). However, this study is not a randomised trial, does not have information on individual people, and may, for example, be confounded by other differences between the Tyrol and the rest of Austria.

When considering population screening programmes the benefits and harms should be assessed, and the benefits should always outweigh the harms. For prostate cancer the benefits of a population screening programme are not fully known (37).

There are significant gaps in our knowledge about the PSA test, prostate cancer and treatment options. The potentially harmful effects of prostate screening are particularly significant. Screening would undoubtedly lead to some men (with indolent disease) suffering from impotence, incontinence, and even death, who would not have done so had screening not been introduced.

For these reasons, the National Screening Committee have recommended that a prostate cancer screening programme should **not** be introduced in England at this time. Instead the Prostate Cancer Risk Management Programme has been introduced so that men who ask about a PSA test can make an informed choice, based on good quality information, about the likelihood of being helped and the likelihood of being harmed.

> To date there is no good evidence to say whether or not screening healthy asymptomatic men would reduce mortality from prostate cancer.

6 Conclusions

Prostate cancer is a significant health problem, mainly affecting older men. There are problems around the early diagnosis and treatment options for the disease, and to date there is no good evidence to say whether or not the introduction of a population screening programme would reduce mortality. Due to the uncertainties surrounding PSA testing, it is important that men who request a test receive balanced information to assist them in making an informed decision about being tested.

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