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Clinical review

Clinically localised prostate cancer

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Prostate cancer is the most commonly diagnosed cancer in United Kingdom men.^{w1} In 2002 it was diagnosed in 32 000 men, and more than 10 000 deaths were attributed to it. Its incidence increased with the introduction of the prostate specific antigen (PSA) blood test, and disease specific mortality has declined. This review provides evidence about risk factors, prevention, detection, natural course, and treatment, with a focus on clinically localised disease, to guide primary care doctors.

What factors increase prostate cancer risk?

Advanced age is the primary risk factor for prostate cancer. About 80% of cases, and 90% of deaths, occur in men over the age of 65.¹ The prevalence of subclinical prostate cancer is high at all ages and greatly exceeds the lifetime risk of dying of prostate cancer (3%). Geographical variation is probably due to racial, dietary, and environmental factors as well as differences in the intensity of cancer detection efforts. Prostate cancer is more common in black men and those with a first degree relative who has had prostate cancer. Mortality may be associated with obesity.² High intake of dairy products and calcium as well as red meat have been claimed to increase risk, though any effect is small.³ Testosterone replacement to treat erectile dysfunction and enhance libido, muscle strength, and wellbeing is popular despite little information about potential risks of prostate cancer or benign prostate problems.^{w2}

Can prostate cancer be prevented?

Few proved strategies exist to prevent prostate cancer. Diets high in soya, selenium, vitamin E, fruits, and lycopenes (tomato based products) may be associated with lower risk of prostate cancer. However, in patients with cancer or preinvasive lesions no association was found between nutritional interventions and cancer mortality or disease-free survival.^{w3} One randomised trial showed

that finasteride, a 5 α reductase inhibitor, reduced the risk of incident prostate cancer at seven years by about six men in 100.⁴ Detected cancers considered high grade, and thus potentially of greater risk for causing morbidity and mortality, were more common in the finasteride than the placebo group.

What signs or symptoms are due to prostate cancer?

Prostate cancer can cause haematuria or urinary obstruction due to local progression. Cancer that spreads outside the gland may result in lower extremity oedema from regional lymphatic obstruction or pain from bone metastasis. However, the vast majority of men with prostate cancer have no symptoms, and their tumours are detected by routine testing. Botherome lower urinary tract symptoms due to benign prostatic obstruction are common in elderly men, result in increased concentrations of prostate specific antigen but do not increase prostate cancer risk.⁵ PSA testing based on the presence of these urinary symptoms is not supported by the evidence.

What detection strategies exist and do they reduce morbidity and mortality?

Digital rectal examination

Digital rectal examination has not been proved to improve morbidity or mortality, and its accuracy is user dependent, with poor reproducibility even among trained clinicians.⁶ About 3-6% of examinations can be expected to find abnormal results that raise suspicions for cancer (induration or nodularity). The examination's predictive value varies substantially with the patient's age, family history of prostate cancer, and PSA concentration. A challenge with testing by digital rectal examination alone is that more than half of the men with prostate cancer detected by the technique will have disease outside the gland at diagnosis.^{w4} Among men with low PSA values (<4.0 ng/ml), the positive predictive value of an abnormal result from digital rectal examination is low, resulting in unnecessary prostate biopsies.⁷ Many of the tumours detected in these men are small, found serendipitously, and of questionable clinical significance.

PSA blood test

Prostate specific antigen is a protein found in the blood of all men. Raised concentrations are associated with

Data sources and selection criteria

We searched Medline and the *Cochrane Library* during August 2006 for randomised trials, systematic reviews, and recent evidence based guidelines from the US Preventive Services Task Force (USPSTF), the American Urological Association (AUA), and the National Institute for Health and Clinical Excellence (NICE)

We searched personal archives of references and the reference lists of relevant articles, including the chapter on prostate cancer (non-metastatic) from *Clinical Evidence* updated in 2003



Extra references w1-w16 are on bmj.com

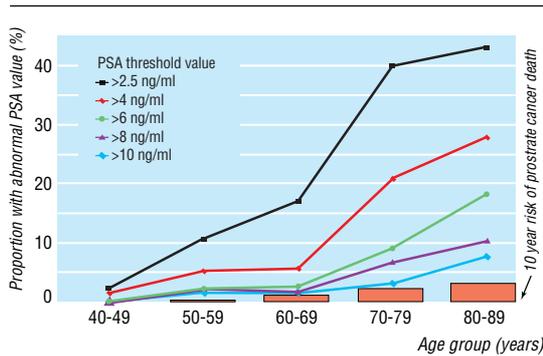


Fig 1 Proportion of US men eligible for prostate specific antigen (PSA) testing who would have abnormal results for different PSA cut-off values. (Adapted from Welch et al⁹)

prostate cancer, but also with enlargement, infection, or inflammation of the prostate. PSA testing detects more cancers at earlier stages and of smaller size than does digital rectal examination. From 1990 to 2002, when PSA testing increased, the annual, age adjusted incidence of prostate cancer in the UK increased nearly twofold.¹¹

A cut-off value of 4.0 ng/ml for normal PSA levels has been proposed as the optimal balance between detecting cancer and avoiding unnecessary extra evaluations. However, lower levels have been detected with many cancers, including high grade, aggressive tumours.⁷ Categorising PSA results as normal or abnormal does not adequately assess prostate cancer risk. PSA values, results from digital rectal examination, family history, age, ethnic origin, and results of prior prostate biopsies are all predictive of prostate cancer risk and risk of high grade disease.⁸ Reducing the PSA threshold that prompts a biopsy detects more cancers and might improve morbidity and mortality from prostate cancer. However, lowering the threshold from 4.0 ng/ml to 2.5 ng/ml would more than double the number of men referred for possible prostate biopsy (fig 1). An individual's risk can be calculated (see www.compass.fhcr.org/edrnci/bin/calculator/main.asp) and may be useful for decision making (fig 2).⁸

Effects of testing on morbidity and mortality

A Cochrane review identified two randomised trials of screening.¹⁰ Both had methodological flaws, but the pooled results found no difference in prostate cancer

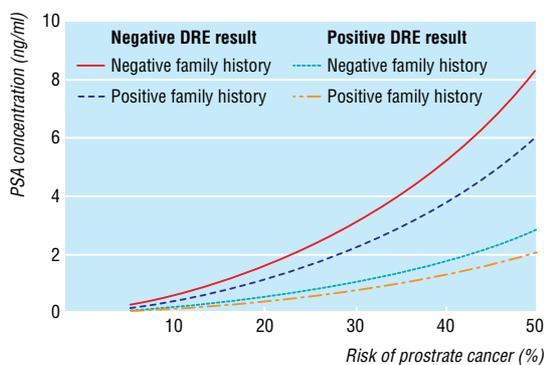


Fig 2 Risk of prostate cancer associated with prostate specific antigen (PSA) concentrations by digital rectal examination result and family history. (Adapted from Thompson et al⁸)

mortality between men randomised to screening with digital rectal examination and PSA testing and the unscreened controls. Case-control studies have generally not found reduced mortality with testing.¹¹ High quality randomised controlled trials in the United States and Europe are currently evaluating whether screening reduces prostate cancer mortality.^{12 13 14}

Testing for prostate cancer is associated with adverse effects including anxiety related to abnormal results; pain, infection, and bleeding from diagnostic prostate biopsies; and detection and treatment of prostate cancers unlikely to cause health problems.^{12 13} Although mortality from prostate cancer has been declining in several countries and some age groups, it is not clear if this is due to increased PSA testing. In the US, where PSA testing is common, the incidence of prostate cancer is about seven times higher than in England and Wales, where testing rates are much lower.

The US Preventive Services Task Force and the UK National Institute for Health and Clinical Excellence and UK Prostate Cancer Risk Management Programme Scientific Reference Group do not recommend routine testing. Men interested in having a test should be informed of the potential but unproved benefits and associated harms.

How is prostate cancer diagnosed and progression risk predicted?

Men with an abnormal test result should be referred for further evaluation and possible prostate biopsy to determine if cancer is present. Multiple tissue cores are removed under transrectal ultrasound guidance. The natural course of a cancer can be estimated from tumour volume, aggressiveness, and disease extent. Volume measures include local stage, number of biopsy cores with cancer, and extent of cancer in the affected cores. The primary measure of aggressiveness is the Gleason histological score: tumours scored 8-10 are considered the most aggressive, while those with scores ≤ 6 are potentially indolent. One classification predicts disease progression without intervention as well as recurrence after treatment:

Low risk—PSA value ≤ 10 ng/ml, Gleason score ≤ 6 , and clinical stage T1c or T2a

Intermediate risk—PSA > 10 -20 ng/ml, Gleason score 7, or clinical stage T2b

High risk—PSA > 20 ng/ml, Gleason score 8-10, or clinical stage T2c.¹⁴

How is prostate cancer treated and what are the risks and benefits?

The commonest treatments include watchful waiting, surgery (radical prostatectomy), external beam and interstitial (brachytherapy) radiotherapy, and early androgen deprivation (see box). Because of a lack of randomised trials, the optimal treatment is not known, and preferred choices and recommendations vary widely. The cancer's natural course, the patient's life expectancy based on age and comorbidities, treatment complications, and patient priorities are important considerations. Factors incorporated into the patient decision process include cancer eradication, adverse effects, doctors' recommendations, convenience, and costs.¹⁵

Treatment options for clinically localised prostate cancer**Watchful waiting (active surveillance, expectant management)**

Active plan to postpone intervention. May involve monitoring with digital rectal examination or PSA blood test and repeat prostate biopsy, with further treatment (curative or palliative) based on patient preference, symptoms, and clinical findings

Potential benefits—No immediate side effects; low initial cost; most men (especially of low to intermediate risk) do not need treatment and survive at least 10 years

Potential risks—Cancer not removed, so could advance, become incurable, and cause death; patients' quality of life could be painfully restricted; other treatments may be necessary, not effective, and have side effects; patients may be too anxious or worried to monitor cancer without treatment

Radical prostatectomy (retropubic or perineal)

Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes. Sometimes done laparoscopically or with robotic assistance and attempt to preserve nerves for erectile function

Potential benefits—May eliminate cancer; generally well tolerated. One randomised controlled trial showed reduced mortality from prostate cancer and metastasis compared with watchful waiting

Potential risks—Hospitalisation for major surgery; operative related death and perioperative cardiovascular complications and bleeding; may not eradicate cancer; long term urinary incontinence, urethral stricture, bladder neck contracture, and bowel and erectile dysfunction

External beam radiation therapy (EBRT)

Multiple doses of radiation from an external source applied over several weeks. Dose and physical characteristics of beam may vary. Conformal radiotherapy uses three dimensional planning systems to maximise dose to prostate cancer and to spare normal tissue

Potential benefits—May eliminate cancer; generally well tolerated; avoids operative risk

Potential risks—Does not remove prostate gland and may not eradicate cancer; 5-8 weeks of outpatient therapy; treatment related death, incontinence, proctitis, diarrhoea, cystitis, erectile dysfunction, urethral stricture, bladder neck contracture, and bleeding. Contraindicated in men with inflammatory bowel disease because of risk of bowel injury. One small, older randomised controlled trial showed greater risk of disease progression compared with prostatectomy

Brachytherapy

Radioactive implants placed under anaesthesia using radiological guidance. Lower dose, permanent implants typically used. External beam "boost" radiotherapy or androgen deprivation sometimes recommended

Potential benefits—May eliminate cancer; generally well tolerated; avoids operative risk; single outpatient session

Potential risks—Does not remove prostate gland and may not eradicate cancer; may not be effective for larger prostate glands or more aggressive tumours; urinary retention, incontinence, impotence, cystitis or urethritis, and proctitis; long term outcomes from representative national sample not reported. Contraindicated in patients with prior transurethral resection of the prostate

Androgen deprivation therapy

Oral or injected drugs or surgical removal of testicles to lower or block circulating androgens

Potential benefits—Avoids risks of prostatectomy and radiotherapy; usually lowers PSA levels and may slow cancer progression

Potential risks—Does not remove prostate cancer and may not eradicate cancer; gynaecomastia, impotence, diarrhoea, osteoporosis, lost libido, hot flushes, and "androgen deprivation syndrome" (depression, memory difficulties, fatigue)

Cryoablation

Destruction of cells through rapid freezing and thawing using transrectal guided placement of probes and injection of freezing and thawing gases

Potential benefits—May eliminate cancer; generally well tolerated; avoids operative risk; single outpatient session

Potential risks—Does not remove prostate gland and may not eradicate cancer; impotence, incontinence, scrotal oedema, pelvic pain, sloughed urethral tissue, prostatic abscess, urethrorectal fistula; no long term outcomes from national sample

Options are associated with short and long term risks including urinary, bowel, and sexual dysfunction, a small risk of treatment related death, as well as cancer spread and death. Treatments vary in the frequency and severity of complications, but all carry some risk. In general, surgery is more likely to cause urinary and sexual dysfunction than radiotherapy, whereas bowel and rectal injury are more common with radiotherapy. Patient priorities are often the primary factor in treatment selection. Patients particularly averse to the risk of cancer may prefer more aggressive treatments at the potential expense of urinary, bowel, or sexual dysfunction. Patients who particularly value quality of life may prefer watchful waiting or less invasive options. Functional issues should be considered. For example, patients with inflammatory bowel disease may be poor candidates for radiotherapy, as bowel symptoms could be exacerbated. Poor bladder function (such as obstructive symptoms or unstable detrusor activity) may be ameliorated by some treatments but exacerbated by others.

Watchful waiting

One report assessed 20 year outcomes from watchful waiting with delayed palliative interventions for cancer detected before the use of PSA testing. Men with low grade disease (Gleason score 2-4) had a minimal risk of dying from prostate cancer in 20 years of follow-up (6 deaths/1000 person years).¹⁶ Men with high grade disease (Gleason score 8-10) had a high probability of dying from prostate cancer within 10 years of diagnosis (121 deaths/1000 person years). Because PSA testing allows detection of cancers some 5-15 years earlier than digital rectal examination, men with PSA detected tumours treated by watchful waiting will probably have better than 20 year disease specific survival.

Radical prostatectomy

Two randomised trials compared surgery with watchful waiting.⁶⁵ Few of the men had tumours detected by PSA testing. One small trial found no difference in survival after 23 years. A more recent and larger study found that surgery improved both disease specific and overall survival by 5% after 10 years: 9% of men assigned to surgery and 14% of those assigned watchful waiting died of prostate cancer (fig 3).¹⁷ Surgery reduced the risk of metastatic and local disease spread but was associated with greater risk of urinary dysfunction (49% v 21%) and sexual dysfunction (80% v 45%). Bowel function, anxiety, and general quality of life were similar. Mortality reduction was limited to men less than 65 years old. Ongoing trials in the US and UK are evaluating surgery, watchful waiting, and radiation therapy in men with primarily PSA screen detected cancers.^{77 78}

External beam radiation therapy

This has been compared with surgery in only one small randomised trial. Despite the findings that disease progression (measured by bone scan and acid phosphatase) was greater in patients treated with radiation therapy, the study is generally considered not applicable to current practice.¹⁸ Recent modifications include high dose conformal radiation therapy, which uses three dimensional planning systems and methods to match radiation treatment to prostate and tumour volumes. Compared with conventional radiotherapy, high dose conformal therapy decreased the rate of recurrence or progression of abnormal PSA values

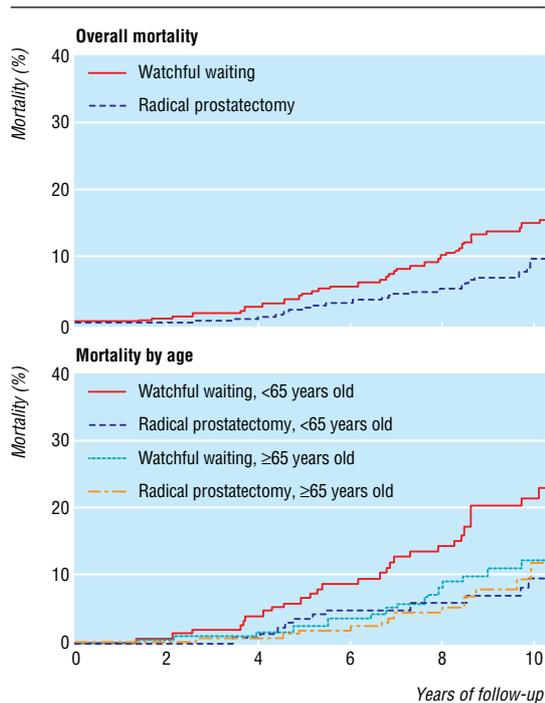


Fig 3 Cumulative mortality from prostate cancer for treatment by radical prostatectomy versus watchful waiting. (Adapted from Bill-Axelsson A et al¹⁷)

(but not mortality) without increasing acute or late serious urinary or rectal complications.^{19 w9}

Brachytherapy

This delivers radiation through the implantation of needles containing small radioactive pellets into the prostate gland under general or spinal anaesthesia. The pellets can be left in place permanently, or temporarily for high dose pellets, and emit a low dose of radiation over several weeks or months. Brachytherapy is used as a primary therapy, in combination with external beam radiation therapy or with androgen deprivation therapy. Brachytherapy has become increasingly used for selected men with low to moderate risk prostate cancers despite no survival data from randomised trials. A review of case series concluded that efficacy and some long term adverse effects were similar to those with surgery or external beam radiation therapy in well selected patients.²⁰ Disease specific quality of life may be lower in patients receiving brachytherapy than in those receiving external beam radiation therapy. Preliminary results of trials comparing different isotopes or adjuvant therapies and other underpowered studies have been published,^{w10-w13} but no conclusions can yet be drawn regarding the relative efficacy versus other treatments as well as optimal forms of brachytherapy.

Androgen deprivation therapy

Use of continuous or intermittent long term androgen deprivation therapy as primary treatment has increased. This approach has not been shown to improve survival, although it lowers PSA concentrations. Among patients with intermediate and high risk localised or locally advanced prostate cancer, addition of adjuvant or neoadjuvant androgen deprivation therapy to external beam radiation therapy, but not to

radical prostatectomy, improves survival.^{21 w14-w16} In addition to treatment costs, adverse effects of androgen deprivation therapy include erectile dysfunction, loss of libido, breast tenderness, hot flushes, depression and mood changes, memory difficulties, fatigue, muscle and bone loss, and fractures.²²

Improving the quality of prevention, testing, and treatment

Given the evidence that finasteride reduces the risk of prostate cancer, doctors should consider providing this information to men over the age of 50. Decisions whether to start prophylactic treatment should take account of patient life expectancy and the long term adverse effects and costs of finasteride. Men interested in testing for prostate cancer should first consult their doctor. Testing can lead to a cascade of unanticipated events if patients do not understand the potential but unproved impact on survival, treatment effectiveness, side effects, and lifelong changes associated with being a "cancer survivor." Rather than recommending for or against prostate cancer testing, doctors should encourage informed decision making among men who inquire about testing, are at least 50 years old, and have a life expectancy of at least 10-15 years. Tools are available to assist in presenting balanced information about the potential benefits and established harms of testing. For men with shorter life expectancy due to age or comorbidities, recommending against testing is likely to lead to superior health outcomes.²³

A review of treatments should include their risks and benefits, incorporating results from any randomised trials and cancer outcomes (see box of treatment options). A multidisciplinary approach to deciding about treatment should be encouraged because recommendations are based in part on doctors' specialties.^{24 25} Decisions can be based on patients' expectations and priorities for outcomes (such as cancer control, anxiety, urinary or

Ongoing research priorities

- Conduct large scale, randomised controlled trials of prostate cancer prevention, detection, and treatment
- Identify biomarkers that can provide reliable identification of cancers requiring treatment
- Standardise reporting of prostate cancer and quality of life outcomes
- Identify measures that improve quality of prostate cancer care, including informed decision making

Unanswered questions

- Do dietary or drug interventions prevent prostate cancer?
- Does screening with PSA blood test and digital rectal examination improve prostate cancer and overall survival?
- What is the comparative effectiveness and adverse effects of different treatments for localised prostate cancer (especially those detected by PSA testing)? Do these vary according to patient, tumour, or provider characteristics?
- Can biomarkers be identified to predict the relative effectiveness of interventions in order to maximise treatment effectiveness while minimising excess detection and treatment?
- What structural and process measures of care are most closely linked to quality outcomes and how can these be improved?

Summary points

Prostate cancer is a common and potentially serious disease

Risk factors include increasing age, family history of prostate cancer, and black race. There are few established prevention strategies

Early detection and treatment may prevent future cancer-related illness, extend life, and provide peace of mind

However, prostate cancer testing, by digital rectal examination and prostate specific antigen testing, can have false positive and false negative results and detects many cancers that would never cause symptoms.

Lower urinary symptoms such as frequency, hesitancy, night time urination, and slow stream do not increase prostate cancer risk but are associated with higher PSA values

The probability that further evaluation with a prostate biopsy will be required as a result of testing is relatively high. Biopsy can cause adverse effects including pain, bleeding, and urinary infection

Treatment options include observation, surgery, radiation, and early hormonal deprivation. Aggressive treatment is needed to realise any benefit from discovery of a tumour, but such treatment may not be necessary or effective

Treatment is associated with a small risk of death and a higher risk of side effects, particularly regarding sexual, urinary, and bowel function

Men with a life expectancy of < 10-15 years (due to advanced age or a serious coexisting condition) are unlikely to benefit from routine testing

Additional educational resources

- Watson E, Jenkins L, Bukach C, Austoker J. *The PSA test and prostate cancer: information for primary care*. Sheffield: NHS Cancer Screening Programmes, 2002
- Aus G, Abbou CC, Bolla M, Heidenreich A, van Poppel H, Schmid H-P, et al. *Guidelines on prostate cancer*. European Association of Urology, 2006. (www.uroweb.nl/files/uploaded_files/guidelines/07%20Prostate%20Cancer.pdf)
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- Agency for Healthcare Research and Quality. Comparison of therapies for clinically localized prostate cancer. (Release date 2007) (<http://effectivehealthcare.ahrq.gov/synthesize/cers.cfm?topic=41>)
- Foundation for Informed Medical Decision Making. www.fimdm.org
- Health Dialog. www.healthdialog.com
- The *Cochrane Library*. www.cochrane.org

sexual function), as well as their life expectancy. Structure and process measures of care reflect attributes of the healthcare setting (such as type of hospital or surgeon's work volume) or describe details of the interactions between provider or patient (such as discussion of alternative treatment risks and benefits). These are modifiable and can influence treatment effectiveness, adverse effects, and patient satisfaction. Initiatives are under way to measure and improve the quality of care for patients with prostate cancer.²⁶

Competing interests: Both authors are chairmen of randomised trials of prostate cancer treatment and prevention referred to in the article.

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