Prostate cancer IV

Screening for prostate cancer

Stephen Frankel, George Davey Smith, Jenny Donovan, David Neal

Epidemiologically, screening is justified by the importance of the disease and the lack of prospects for primary prevention, but evidence from natural history is unhelpful since men are more likely to die with, rather than from, prostate cancer. The available screening tests do not always detect men whose lesions could result in future morbidity or mortality. Evidence is limited for the benefits of treatment for localised cancers detected through screening, whereas the evidence for harm is clear. Observational evidence for the effect of population screening programmes is mixed, with no clear association between intensity of screening and reduced prostate cancer mortality. Screening for prostate cancer cannot be justified in low-risk populations, but the balance of benefit and harm will be more favourable after risk stratification. Prostate cancer screening can be justified only in research programmes designed to assess its effectiveness and help identify the groups who may benefit.

Few issues in health care are as controversial as prostate cancer screening. The issue has been well debated,[1] but the absence of adequate evidence is compensated for by energetic advocacy that goes beyond specialist circles. For example, when the editors of the *Western Journal of Medicine* wrote a mild piece for the *San Francisco Chronicle*[2] questioning the value of screening, the newspaper, the authors, and their university employers were bombarded by vitriolic e-mails because the piece "challenged the widespread belief in America that every man should know his PSA [prostate-specific antigen]".[3] Pressure, purportedly public, yet often stemming from specific interest groups or enthusiastic journalists, is constantly applied to introduce screening and then to reduce screening intervals and extend age ranges. The published work also contains many flawed analyses and naive polemic. The same evidence has resulted in differing approaches on either side of the Atlantic and from different groups in the same country. For example, in the USA, the *Guide to Clinical Preventive Services* issued by the US Preventive Services Task Force argues against any prostate screening,[4] whereas the American Urological Association recommends that all men aged 50 years and older who can be expected to live for another 10 years (the vast majority) should be offered prostate screening.[5] In this context, the recommendation of the American College of Preventive Medicine that men should be fully informed of the risks and benefits of screening and then asked to make up their own minds[6] is perhaps disingenuous when it is clearly difficult for specialist advisers to know the best approach. Here, we review the evidence about prostate cancer screening, and discuss probable future developments.

Judging the merits of screening

Discussions of screening are conventionally based on the criteria described by Wilson and Jungner.[7] The enduring authority of that 1968 account partly reflects the value of its contents, but also the lack of fresh thinking since that time. This area of health policy is unsatisfactory in that support for, or dismissal of, the worth of screening programmes is dominated by advocacy rather than scientific debate. The recurrent confusion in screening policy relates to three aspects of the Wilson and Jungner criteria. First, there is no insistence on evidence from randomised controlled trials. Second, the criteria are listed as individually discrete interests with no attempt to specify what constitutes part or full satisfaction of the individual criteria or what combination of part satisfaction of these criteria would justify screening. The biases inherent in the observational evidence that is available mean that the Wilson and Jungner criteria offer a framework for assertion, but can hinder rather than help a decision that should be reliant on robust evidence. The decision on whether to screen is presented as a binary option built on a series of binary options (important or not important, etc) when screening is in reality a programme of risk reduction in which every criterion must interact with others. For example, test performance and treatment effectiveness are inseparable, since treatment effectiveness can differ according to the pathological characteristics of those identified for treatment; if men whose microcellular changes might progress to symptomatic prostate cancer could be identified precisely, treatment effectiveness would improve substantially. Third, the importance of non-technical influences on public policy is not acknowledged. Furthermore, if the criteria cannot support robust decision-making, the intuitive value of early detection and treatment is not readily countermanded. However great the risk reduction is, risk will remain. The lack of public recognition of this fact is one basis for public disquiet about screening. The second two issues have only been partly addressed in more recent screening

Search strategy and selection criteria

Our review of the published work is built on previous systematic reviews of prostate cancer screening, supplemented by an update of subsequent research from reviews and bibliographies of published articles and publications identified from major bibliographic sources, including Medline, Embase, and Web of Science, focusing on issues relating to MeSH terms "prostatic neoplasms" and "mass screening", and text terms "prostate cancer" and "screening".

Lancet 2003; **361:** 1122–28

Department of Social Medicine, University of Bristol, Canynge Hall, Bristol BS8 2PR, UK (Prof S Frankel DM, Prof G Davey Smith DSc, Prof J Donovan PhD); **Oncology Centre, Addenbrooke Hospital, Cambridge, UK** (Prof D Neal FRCS)

Correspondence to: Prof George Davey Smith (e-mail: zetkin@bristol.ac.uk)

checklists (panel 1), though when existing screening programmes do not satisfy even a moderately restrictive interpretation of several criteria, the criteria tend to be ignored.

Epidemiology and natural history

The epidemiology of prostate cancer has been discussed by Henrik Grönberg earlier in this *Lancet* series.[9] Here, we focus on those issues most relevant to screening: the importance of the disorder, the potential for primary prevention, and the extent to which the natural history of prostate cancer renders it amenable to screening.

Importance

Prostate cancer is the most commonly diagnosed non-skin cancer in most developed countries and could become the commonest male cancer worldwide.[10] In terms of male cancer deaths it is second only to lung cancer, with some 41 000 deaths per year in the USA,[11] and more than 8500 deaths a year in the UK.[12]

Potential for primary prevention

Few cancers vary as widely between and within countries as prostate cancer. Thus, that analytical epidemiology has identified no simple causes is frustrating. Genetic factors are clearly important in prostate cancer, although major susceptibility genes account for only 5–10% of prostate cancer cases.[13,14] Several common polymorphisms are associated with a modest increase in disease risk,[9,14] but some of the findings are inconclusive and even if confirmed, the magnitude of effect would not justify inclusion of genotyping for these polymorphisms within a screening programme. Diet also has some effect on prostate cancer, but none of the findings approaches the robustness needed for public recommendations. Chemoprevention might emerge as a valuable adjunct or alternative to screening, and is under investigation in trials of finasteride[15] and selenium and vitamin E.[16] The epidemiological associations between height and prostate cancer,[17] and between measured insulin-like growth factor (IGF)-I and prostate cancer,[18] are important for understanding pathogenesis, but, like the other causes considered here, offer no immediate prospects for primary prevention. Secondary prevention through screening is therefore the only population-based approach available.

Natural history

The natural history of prostate cancer is uncertain because men are much more likely to die with, rather than of, prostate cancer.[19] Tumour foci have been identified in 30–40% of men aged 60 years,[19] though the median age of onset of symptoms is 72 years.[20] Although the life-time risk of having microscopic prostate cancer for a man of 50 years is 42%, the risk of his dying of prostate cancer is about 3%.[19] Only 16% of those with disease detected by screening benefit from radical treatments, since their disease would not otherwise have compromised their life expectancy or quality of life.[21] Thus, 84% of radical

Panel 1: **Criteria for appraising the viability, effectiveness, and appropriateness of a screening programme**[8]

The disorder

The disorder should be an important health problem

The epidemiology and natural history of the disorder should be adequately understood and there should be a detectable risk factor, or disease marker, and a latent period or early symptomatic stage

All cost-effective primary prevention interventions should have been implemented as far as practicable

The test

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 cut-off level 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 result and on the choices available to those individuals

The treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

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 disorder and patient outcomes should be optimised by all health-care providers before participation in a screening programme

The screening programme

There must be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity

There should be evidence that the complete screening programme 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 should be economically balanced in relation to expenditure on medical care as a whole (ie, value for money)

There must 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 made available before the screening programme starts

All other options for managing the disorder should have been considered

Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice

Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated

Decisions about these variables should be scientifically justifiable

Panel 2: **Strategic questions about prostate cancer screening**

Question	Screening worthwhile if:	Screening not supportable if:
Can we identify with sufficient precision those men whose cancers will impinge on their lives?	The early cellular changes detected through screening are commonly the precursors of later aggressive cancers that would become manifest during the man's lifetime	There is an uncertain relation between common microcellular changes and later aggressive cancers that would become manifest
Is radical treatment of screen-detected prostate cancer effective and justified?	Radical treatment for localised cancer extends life and does not unduly damage quality of life	Such treatments expose too many men to complications when their prostate cancer would not have become apparent to them during life
Is there evidence that existing screening population programmes are effective?	Trends in prostate cancer data support the effectiveness of early radical treatment	Trends arise largely from a combination of trends of largely unknown causes

treatments for localised disease are done with no prospect of benefit. Within the European Randomised Study of Screening for Prostate Cancer,[22] the cumulative incidence of prostate cancer was 14·6 times greater than the death rate, another indication that disease detected through screening is a more inclusive category than progressive disease. Tumour progression is difficult to predict because of the wide variability found in progression with tumours of different grades. Between 1971 and 1984, men diagnosed with localised prostate cancer in Connecticut, USA who were treated conservatively faced a 4–7% chance of dying from this disease within 15 years of diagnosis with tumours if they had Gleason scores of 2–4, compared with 18–30% for those who had the most common Gleason score of 6, and 60–80% for those with the highest scores of 8–10 (panel 2).[23]

Apart from some small series, data for the natural history of prostate cancer therefore comes from cross-sectional studies, which are inadequate. More refined knowledge will emerge over the next 10–15 years from the active monitoring group of ProtecT[24] and other studies, but knowledge of the natural history of prostate cancer might not help to inform choices for individual care or screening policy for some time.

The test

Tests have no meaning without clarity of purpose. The main issue is therefore not the screening test itself, but a precise definition of what is to be identified. In the case of screening, it is not cancerous prostate tissue that is being sought; the aim is to identify men who are asymptomatic and would otherwise die or be disadvantaged by untreated prostate cancer in the future, perhaps in 10 or 15 years. Part of the confusion is that these two different categories—potentially and definitely undesirable pathological changes—are frequently merged. For example, the editorial[25] accompanying the Scandinavian Prostatic Cancer Group trial claims that of men who test positive at screening, only those who are too old or sick for surgery should be denied radical prostatectomy. However, this conclusion is not supported by the trial, since most men within the trial did not have their tumours detected through screening. A distinction in terminology between screened and clinical disease would help to make such misunderstandings less likely. If only 9% of men with localised prostate cancer are likely to die of prostate cancer within 15 years, is it reasonable to classify all the 91% who will not die as having the disease?[26]

The digital rectal examination (DRE) has little value as a screening test.[27] The main test on which developments in management of prostate cancer depend is the serum concentration of prostate specific antigen (PSA). PSA concentrations relate to age, prostate size, and the presence of prostate cancer, but can also be raised after ejaculation, prostate biopsy, surgery, or prostatitis. PSA is not diagnostic of prostate cancer—such diagnosis can be made only after a biopsy, which itself brings the risk of complications, commonly of discomfort and bleeding, and more rarely sepsis. The validity of PSA as a test for risk of death from prostate cancer is unknowable because the gold standard—presence of cancerous changes, clinically apparent or not—is attainable only through biopsy, and because the future relevance of such changes is unknown.

Whatever the cut-point, 8–10% of men aged between 50 and 69 years will have a raised PSA result that will indicate a biopsy. What constitutes an abnormal PSA result is controversial. Many organisations favour a cut-off of 4 μg/L, and the positive predictive value at this concentration can be reasonable—26% in the Finnish trial[28] and good validity in a Finnish study[29] based on links between a collection of serum samples and cancer registry data (sensitivity 44%; specificity 94%). However, up to two-thirds of cancers are missed at the 4 μg/L concentration.[30] In a community-based study[31] of serial screening, 22% of men older than 50 years with PSA concentrations between 2·6 and 4·0 μg/L had prostate cancer. In the European Randomised Study of Screening for Prostate Cancer (ERSPC),[32] 36·5% of detectable prostate cancers were identified in the 87·5% of men who had PSA concentrations lower than 4 μg/L. In the Scandinavian trial[33] 15% of enrolled men had PSAs of less than 4 μg/L. The cancers that are missed might not be irrelevant: half the cancers in which radical prostatectomy was done, even with a PSA less than 4 μg/L, had a Gleason score of higher than 7. Such concerns about an appropriate cut-off point have led to biopsies now being done on all men with PSA of 3 μg/L and higher in the ERSPC trial.[22]

The probability of death in relation to presentation has been investigated,[34] but such analyses could not predict an individual's outcome. Specificity can be increased, but with reduced sensitivity, through use of free PSA, total PSA, or both.[35] The prognostic value of PSA doubling time and PSA velocity, among other measures, are being assessed. Many microscopic tumours detected by biopsy after PSA testing are unrelated to PSA for two reasons. First, small tumours, less than 1 mL, will probably not result in a raised PSA, which could be more related to the bulk of the prostate gland. Second, microscopic tumours and raised PSA are very common, and will thus often occur together by chance.[36] Thus, if small prostate cancers are important, then it is unacceptable that many are missed; if smaller tumours are not important, then radical treatments are being offered unnecessarily.[1] Few disorders have such common precursors. Because so many men

have histological prostate cancer[19] screening may not have any relation to outcome, especially when the outcome of treating a disorder that has such extended untreated survival may not be known for 10 years or longer. Clinical staging of prostate cancer is also difficult; 25–50% of tumours are understaged at diagnosis. It is only possible to determine true pathological staging in cases treated with radical surgery.

The weakness of the case for generalised prostate cancer screening centres on the poorly defined nature of the group identified for treatment. Without stratification, the current predictive values are poor. Once a differentiated natural history can be described in which those whose disease is likely to progress can be distinguished from those whose pathology presents limited risk in terms of function or survival, the ratio of harm to benefit will shift advantageously. Cancers and their behaviour are classified mostly on the basis of morphology assessed by conventional light microscopy. This process is changing and risk stratification will probably be based on genomic and proteomic studies coupled with rigorous bioinformatics, which will greatly change the taxonomy of tumours.[37]

The treatment

Exposing healthy people to treatments with specific hazards and uncertain benefits is unacceptable, especially when the benefits of treating asymptomatic individuals identified through screening differs from treating manifested disease.[38] The fundamental, and unresolved, issue is what proportion of cancers identified through screening would have progressed to become life-threatening. Survival after treatment for advanced disease might be poor because the disease has spread. Survival after treatment for small confined tumours might be good because such local changes had no implications for length or quality of life. Those with small confined tumours are becoming more and more important when survival without treatment is good;[39] over a quarter of surgery in the USA is for tumours of less than 0·5 cm, and 72% of tumours will be confined to the prostate.[40]

Panel 3: **TNM classification (and Gleason scores*)**

Classification	Description
T1	**Not palpable or visible**
T1a	<5% involved on a TURP sample
T1b	>5% involved on a TURP sample
T1c	Needle biopsy positive (usually diagnosed because of high PSA)
T2	**Confined within prostate**
T2a	<half of one lobe
T2b	>half of one lobe
T2c	Both lobes
T3	**Outside prostate**
T3a	Extracapsular invasions
T3b	Seminal vesicle(s)
T4	Fixed or invades adjacent structures: bladder neck, external sphincter, rectum, levator muscles, pelvic wall
N	**Nodal status**
N0	No nodes
N1	Regional lymph node(s) positive
M	**Metastatic status**
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Pathological grade in prostate cancer is best assessed by the Gleason *grading system, to predict future behaviour. Predicting the final Gleason score of the actual tumour (following radical prostatectomy) from a biopsy is not easy; there is usually underscoring on the biopsy. Taking the proportion of the needle biopsy affected by tumour (say 10% *vs* 80%) allows some prediction that the tumour might be organ confined if and when surgery is done.

Treatment options have been described previously in this series.[41] Radical prostatectomy for localised prostate cancer will in many cases remove the risk of death from this disease, but how can this procedure be justified in men who are otherwise healthy? 2–5% of men have severe incontinence after surgery,[42] and between 10% and 90% become impotent,[43,44] with an average of about 70%. In the Scandinavian trial,[45] 80% of men in the radical prostatectomy group reported erectile dysfunction and 50% had urinary leakage. In their treatment algorithm, Ashesh Jani and Samuel Hellman[41] offer guidance in the choices between hormone therapy, neoadjuvant hormone therapy, external-beam radiotherapy, interstitial brachytherapy, and radical retropubic prostatectomy, but the evidence in guiding treatment for early localised disease is tentative. Published evidence has an uncertain effect on clinical practice: specialists generally recommend the treatment that they themselves can offer. In the USA and the UK, urologists offer radical prostatectomy, whereas oncologists and radiologists offer radical radiotherapy.[46–48]

Many of the studies of treatment that have been published are too small, are observational, and are otherwise insufficiently robust. The findings of the Scandinavian trial[33] are therefore fundamentally important. 695 men with early prostate cancer were randomised to either watchful waiting or radical prostatectomy, and were followed up for a median of 6·2 years. Prostatectomy lowered the risk of death from prostate cancer at 8 years (relative hazard 0·5, 95% CI 0·25–0·84), the development of distant metastases, and the rates of local progression, but no significant difference in overall mortality was seen (0·83, 0·57–1·2). However, the study has little relevance to the issue of whether to screen since only 5% of these men were detected through screening, and 76% had palpable stage T2 tumours (panel 3). With no significant improvement in all-cause mortality and major quality of life implications, radical prostatectomy remains a controversial procedure. Some important questions remain about this study. For instance, 31 of 348 men managed by watchful waiting died of prostate cancer compared with 16 of 347 assigned to surgery; in view of the advanced average stage of the cancers, this early benefit was surprising. 23 men who should have undergone surgery did not because positive lymph nodes were identified; early hormonal ablation in this small subgroup might have partly inflated the apparent benefit of surgery. This important study thus offers no justification for screening programmes that expose men who might never be aware of the pathological changes within their prostates, to uncertainties about outcome, and to certainties about the disagreeable nature of the treatment process.

At present, men are offered an informed choice. The most informed observer can only point to uncertainty. In this situation the only responsible position is that men who are included in such programmes should be offered treatments in trials that will reduce such uncertainty.[24] It is possible to communicate to men the level of uncertainty, though success depends on extensive discussion with clinicians trained to communicate the risks and benefits.

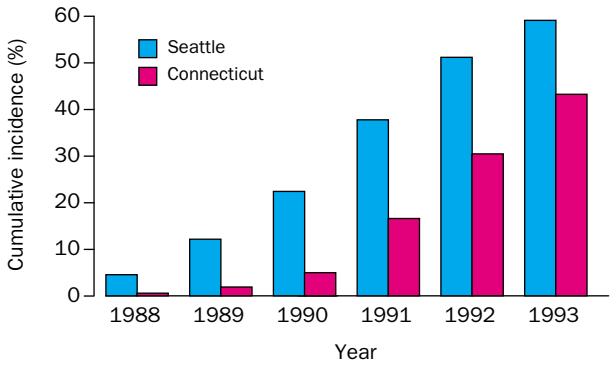

Figure 1: **Unadjusted cumulative incidence of first prostate specific antigen (PSA) test for study cohort members in the Seattle-Puget Sound and Connecticut areas, 1988–93**
Reproduced with permission from Lu-Yao and colleagues.[69]

Effectiveness of screening programmes

In the USA, the reported incidence and mortality of prostate cancer have risen and then fallen[49] in ways that have been attributed to PSA screening and treatment changes.[50–52] Similar trends have been seen in Austria.[53,54] In Quebec City, Canada, a 67% reduction in deaths was attributed to screening.[55] How strong are these data in suggesting that screening affects mortality? Some of the assertions of effectiveness are naive. For example the findings of the Quebec trial[55] are probably the product of several biases in flawed analyses.[56,57] Nevertheless, in the absence of randomised evidence on the effectiveness of screening, observational data carry a greater burden of evidence than might be appropriate.

Before the 1980s, prostate cancer mortality was increasing in most industrialised countries,[58] and then began to fall in some regions where screening was intensive.[59] However similar decreases have been recorded in the UK[60] and the Netherlands[22] over the same period, though levels of PSA testing have been lower. A balanced view of this picture requires a broad view of national trends where screening practices have differed. A study of prostate cancer in 24 countries showed a greater than five-fold range in mortality.[61] Mortality increased steadily by 1–2% over the period 1979–97 in most countries, though

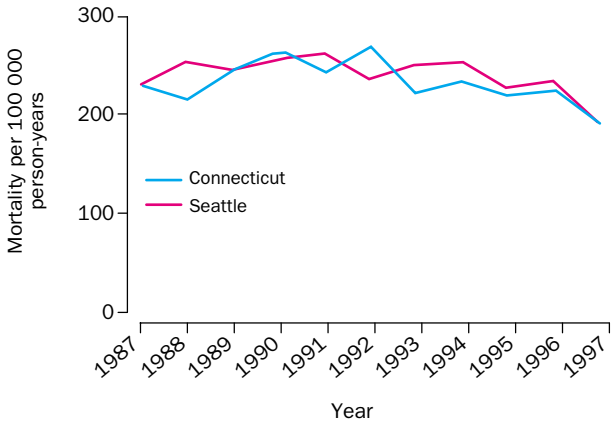

Figure 2: **Age-adjusted prostate cancer mortality per 100 000 person years for men in Seattle-Puget Sound and Connecticut on the basis of cross sectional data, 1987–97**
Data adjusted to the age composition of the entire cohort: 48·3% aged 70–74 years, 33·3% aged 75–79 years, 18·4% aged 80–84 years as of Jan 1, 1992). (US data by SEER region, age, and race provided by L Ries, Cancer Statistics Branch, National Cancer Institute). Reproduced with permission from Lu-Yao and colleagues.[69]

in Canada, USA, Austria, France, Germany, Italy, and the UK, mortality decreased from 1988 to 1991. Aspects of these trends can be artifactual, since prostate cancer is readily misattributed and PSA testing will have detected cases at an earlier stage.[60,62–64] Intensive application of effective treatments can affect mortality trends, but practice differs between countries. Even in the USA it is difficult to attribute major population effects to treatment without making implausibly optimistic assumptions,[65] although hormonal treatment of men with advanced local or metastatic disease could also have affected mortality. In the USA, intensive screening has been associated with falling mortality, but similar decreases in the UK are not associated with screening, the intensive screening in Australia is not associated with falling mortality,[66,67] and the fall in mortality in Quebec is difficult to ascribe to screening when the trends within birth cohorts are analysed.[68] Therefore, whether favourable mortality trends can be ascribed to PSA screening is difficult to determine. A comparison within the USA showed much more rapid uptake of PSA testing in the Seattle-Puget Sound than in Connecticut (figure 1),[69] but no difference in mortality, even with plausible time-lags (figure 2).[69] This lack of effect of high uptake of PSA testing on mortality is not compatible with the magnitude or time course for improvements that have been projected from comparisons of trends in PSA testing and mortality across the USA.

The difficulties with calculating causation and treatment benefits on the basis of observational data are well known.[70] A sceptical stance should be taken before assuming that any association between trends in prostate cancer mortality and prostate cancer screening have any underlying causal relation. The evidence that is available cannot support such a causative link, and the conclusion has to be that we must await adequate trial data.

Conclusions

The balance of proof must be high to justify exposing men older than 50 years to a process where, of 1 million men, about 110 000 with raised PSAs will face anxiety over possible cancer, about 90 000 will undergo biopsy, and 20 000 will be diagnosed with cancer. If 10 000 of these men underwent surgery, about ten would die of the operation, 300 will develop severe urinary incontinence, and even in the best hands 4000 will become impotent. The number of men whose prostate cancer would have impinged on their lives is unknown. Strong evidence that might support the view that screening is worthwhile is absent. The epidemiological issues can be reduced to three questions, as shown in panel 2. On the basis of the evidence, national programmes of prostate cancer screening are not justified, yet routine prostate cancer screening is commonly advocated,[71,72] and even where concern is expressed about the wisdom of routine screening, the ambiguous recommendations that emerge offer little counterweight to the momentum behind routine PSA testing.[73–75]

The fact that routine prostate cancer screening is done in some countries outside an experimental framework, and is advocated energetically in those countries that are resisting its implementation, is a striking instance of therapeutic optimism, or that "hope springs eternal in the human breast".[76] In these purportedly evidence-based times naive use of inappropriate data can be surprising, though the intuitive merits of removing cancerous tissue finds public sympathy. Rather than policy following evidence, implicit policy preferences guide decisions about what is advisable.[77] The same evidence is available on each side of the Atlantic to the public, to practitioners,

and to policy makers, yet practice differs greatly between the USA and Europe. In the UK most medical decision-making is centralised, so that the technical arguments for and against screening can have a greater effect. The more entrepreneurial medical culture in the USA, allied to a more engaged public and perhaps commercially motivated lobbying,[2] make the case for caution more vulnerable.

Here, we have discussed the current situation, but the ratio of benefit to harm will probably change during the coming years as more refined markers, including genetic markers, of risk emerge and it becomes possible to stratify men according to early evidence of progression. However, in view of present performance levels of PSA testing and potential treatment effects it might be optimistic to expect to see benefits that are large enough to be detected in a randomised trial of plausible magnitude. The Norwegian Urological Cancer Group,[78] for example, has decided not to participate in the ERSPC because of such concerns. In such a situation the decision to set up a study that will not yield a result for many years is a difficult one. The trial could be overtaken by improvements in technology (either in screening, prediction of prognosis, or treatment) and its findings will not be applicable when it is completed. Instigation of a trial that is destined to fail could mitigate against introduction of new technologies when they have been developed, since they would be associated with the ineffective methods. In cholesterol lowering to prevent coronary heart disease, for example, the fact that early clinical practice and studies involved drugs later found to be harmful—triparanol and clofibrate—may have delayed acceptance and uptake of the much more effective statin treatment.[79]

Prostate cancer screening is relevant to four groups of men.[78] First, those whose cancer emerges clinically, whose outcome is not affected by being treated at that time, and for whom screening would not affect their situation. Second, those whose cancer is advancing so rapidly that screening would not improve their outcome. Third, those whose screen-detected disease would otherwise never have manifested and who are exposed to unnecessary treatment. Fourth, asymptomatic individuals who receive beneficial treatment that otherwise would have been denied. The difficulty in identifying this fourth group renders the current case for screening very weak. However, as the capacity to identify men in this fourth group increases, the case will strengthen accordingly.

The development of prostate cancer screening has three phases. After PSA was identified as a possible predictor, a period of experimentation and naive assertion began.[80] A combination of factors led to promotion and either implementation, or resistance to, national screening programmes, resulting in the second phase where the scale of activity in some countries, especially the USA, is substantial, but the evidence base is inadequate. We are now entering a third phase where the substantial investment in trials of screening and treatment will result first in experimental data on which to base effectiveness, but, more importantly, refinement of the predictive power of testing. The nub of the issue is risk stratification. The absolute risk of death from prostate cancer is low—1·33% in the Netherlands for example.[81] Here even a very optimistic risk reduction of 25% would produce an absolute risk reduction of 0·33%. Over three screening rounds about 900 men would be exposed to the hazards of prostate cancer management to delay one death. However, this situation will change once high-risk populations can be identified. When it becomes possible to target with greater probability those men whose cancers will later threaten their wellbeing, prostate cancer screening will properly become as unexceptionable as, say, screening for phenylketonuria. But, at the moment there is no scientific case for doing routine prostate cancer screening outside research programmes designed to assess its effectiveness and help identify the groups who might benefit.[82]

Conflict of interest statement
None declared.

Acknowledgments
J Donovan and D Neal are principal investigators on the Protect Study, funded by the NHS Health Technology Assessment programme. The study sponsor had no role in writing this report.

References

1 Neal DE, Donovan JL. Prostate cancer: to screen or not to screen? *Lancet Oncol* 2000; **1:** 17–24.
2 Yamey G, Wilkes M. Prostate cancer screening: is it worth the pain? *San Francisco Chronicle* Jan 18, 2002.
3 Ferriman A. Advocates of PSA testing campaign to silence critics. *BMJ* 2002; **324:** 255.
4 DiGuiseppi C, ed. US Preventive Services Task Force. Guide to clinical preventive services. Baltimore: Williams and Wilkins, 1996.
5 Cookson MM. Prostate cancer: screening and early detection. *Cancer Control* 2001; **8:** 133–40.
6 Ferrini R, Woolf SH. American College of Preventive Medicine practice policy. Screening for prostate cancer in American men. *Am J Prev Med* 1998; **15:** 81–84.
7 Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Paper Number 34. Geneva: World Health Organization, 1968.
8 The UK National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. http://www.doh.gov.uk/nsc/library/lib_ind.htm (accessed Jan 15, 2003).
9 Grönberg H. Prostate cancer epidemiology. *Lancet* 2003; **361:** 859–64.
10 Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000: the global picture. *Eur J Cancer* 2001; **37** (suppl)**:** S4–66.
11 von Eschenbach A, Ho R, Murphy GP, et al. American Cancer Society guidelines for early detection of prostate cancer. *Cancer* 1997; **80:** 1805–07.
12 Office for National Statistics. 1993 Cancer statistics: registrations. London: Stationery Office, 1999.
13 Stanford JL, Ostrander EA. Familial prostate cancer. *Epidemiol Rev* 2001; **23:** 19–23.
14 Coughlin SS, Hall IJ. A review of genetic polymorphisms and prostate cancer risk. *Ann Epidemiol* 2002; **12:** 182–96.
15 Coltman CA, Thompson IM, Feigl P. Prostate Cancer Prevention Trial (PCPT) update. *Eur Urol* 1999; **35:** 544–47.
16 Klein EA, Thompson IM, Lippman SM, et al. SELECT: the next prostate cancer prevention trial. *J Urol* 2001; **166:** 1311–15.
17 Gunnell D, Okasha M, Davey Smith G, Oliver SE, Sandhu J, Holly JMP. Height, leg length and cancer risk: a systematic review. *Epidemiol Rev* 2001; **23:** 313–42.
18 Pollak M. Insulin-like growth factors and prostate cancer. *Epidemiol Rev* 2001; **23:** 59–66.
19 Whitmore WF Jnr. Localised prostate cancer: management and detection issues. *Lancet* 1994; **343:** 1263–67.
20 Meikle AW, Smith JA, Epidemiology of prostate cancer. *Urol Clin North Am* 1990; **17:** 709–19.
21 McGregor M, Hanley JA, Boivin J-F, et al. Screening for prostate cancer: estimating the magnitude of overdetection. *Can Med Assoc J* 1998; **159:** 1368–72.
22 Schröder FH, Wildhagen MF. Screening for prostate cancer: evidence and perspectives. *BJU Int* 2001; **88:** 811–17.
23 Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55–74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998; **280:** 975–80.
24 Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ* 2002; **325:** 766–70.
25 Walsh PC. Surgery and the reduction of mortality from prostate cancer. *N Engl J Med* 2002; **347:** 839–40.
26 Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 1995; **274:** 626–31.

27 Reissigl A, Pointner J, Horninger W, et al. PSA-based screening for prostate cancer in asymptomatic younger males: pilot study in blood donors. *Prostate* 1997; **30:** 20–25.

28 Maatanen L, Auvinen A, Stenman U-H, et al. European randomised study of prostate cancer screening: first-year results of the Finnish trial. *Br J Cancer* 1999; **79:** 1210–14.

29 Hakama M, Stenman U-H, Aromaa A, Leinonen J, Hakulinen T, Knekt P. Validity of the prostate specific antigen test for prostate cancer screening: follow-up study with a bank of 21 000 sera in Finland. *J Urol* 2001; **166:** 2189–92.

30 Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schröder FH. Predictors for biopsy outcome in the European Randomized Study of Screening for Prostate Cancer (Rotterdam region). *Prostate* 1999; **39:** 316–22.

31 Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2·6 to 4·0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. *JAMA* 1997; **277:** 1452–55.

32 Schröder FH, van der Cruijsen-Koeter I, Koning HJ, et al. Prostate cancer detection at low prostate specific antigen. *J Urol* 2000; **163:** 806–12.

33 Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002; **347:** 781–89.

34 Johansson JE, Holmberg L, Johansson S, Bergstrom R, Adami HO. Fifteen-year survival in prostate cancer: a prospective, population-based study in Sweden. *JAMA* 1997; **277:** 467–71.

35 Bangma CH, Rietbergen JBW, Kranse R, et al. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. *J Urol* 1997; **157:** 2191–96.

36 Collins MM, Ransohoff DF, Barry MJ. Early detection of prostate cancer-serendipity strikes again. *JAMA* 1997; **278:** 1516–19.

37 Caldas C, Aparicio SA. Cancer: the molecular outlook. *Nature* 2002; **415:** 484–485.

38 Davey Smith G, Egger M. Who benefits from medical interventions? *BMJ* 1994; **308:** 72–74.

39 Johansson JE, Adami HO, Andersson S-O, Bergström R, Krusemo UB, Kraaz W. Natural history of localised prostatic cancer: a population-based study in 223 untreated patients. *Lancet* 1989; **1:** 799–803.

40 Carter HB, Sauvageot J, Walsh PC, et al. Prospective evaluation of men with stage T1c adenocarcinoma of the prostate. *J Urol* 1997; **157:** 2206–09.

41 Jani AB, Hellman S. Clinical decision-making in early prostate cancer. *Lancet* 2003; **361:** 1045–53.

42 Weldon VE, Tavel FR, Neuwirth H. Continence, potency and morbidity after radical perineal prostatectomy. *J Urol* 1997; **158:** 1470–75.

43 Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. *JAMA* 2000; **283:** 354–60.

44 Siegel T, Moul JW, Spevak M, Alvord G, Costabile RA. The development of erectile dysfunction in men treated for prostate cancer. *J Urol* 2001; **165:** 430–35.

45 Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; **347:** 790–96.

46 Fowler FJ, McNaughton Collins M, Albertsen PC, Zietman A, Elliott D, Barry M. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. *JAMA* 2000; **283:** 3217–22.

47 Donovan JL, Frankel S, Faulkner A, Gillatt D, Hamdy FC. Dilemmas in treating early prostate cancer: the evidence and a questionnaire survey of consultant urologists in the UK. *BMJ* 1999; **318:** 299–300.

48 Hanna CL, Mason MD, Donovan JL, Barber JP. Clinical oncologists favour radical radiotherapy for localised prostate cancer: a questionnaire survey study. *Br J Urol Int* 2002; **90:** 558–60.

49 Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer. Part 1: evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. *J Natl Cancer Inst* 1999; **91:** 1017–24.

50 Farkas A, Schneider D, Perrotti M, et al. National trends in the epidemiology of prostate cancer, to 1994: evidence for the effectiveness of PSA screening. *Urology* 1973; **52:** 444–48.

51 Littrup PJ. Future benefits and cost-effectiveness of prostate carcinoma screening. *Cancer* 1997; **80:** 1864–70.

52 Hoeksema MJ, Law C. Cancer mortality rates fall: a turning point for the nation. *J Natl Cancer Inst* 1996; **88:** 1706–07.

53 Horninger W, Reissigl A, Rogatsch H, et al. Prostate cancer screening in the Tyrol, Austria: experience and results. *Eur J Cancer* 2000; **36:** 1322–35.

54 Bartsch G, Horninger W, Klocker H, et al. Tyrol Prostate Cancer Screening Group. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001; **58:** 417–24.

55 Labrie F, Candas B, Dupont A, et al. Screening decreases prostrate cancer death. First analysis of the 1988 Quebec prospective randomised controlled trial. *Prostate* 1999; **38:** 83–91.

56 Alexander JE. Screening decreases prostrate cancer death: first analysis of the 1988 Quebec prospective randomised controlled trial. *Prostate* 1999; **40:** 135–36.

57 Boer R, Schröder F. Quebec randomised controlled trial on prostate cancer screening shows no evidence for mortality reduction. *Prostate* 1999; **40:** 130–34.

58 Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer* 2000; **85:** 60–67.

59 Mettlin CJ, Murphy GP. Why is the prostate cancer death rate declining in the United States? *Cancer* 1998; **82:** 249–51.

60 Oliver SE, Gunnell D, Donovan JL. Comparison of trends in prostate cancer mortality in England and Wales and the USA. *Lancet* 2000; **335:** 1788–89.

61 Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the "PSA era". *Int J Cancer* 2001; **92:** 893–98.

62 Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *J Urol* 2000; **163:** 519–23.

63 Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison non prostate cancer cohort. *J Natl Cancer Inst* 2000; **92:** 613–21.

64 Feuer EJ, Merrill RM, Hankey BF. Cancer surveillance series: interpreting trends in prostate cancer. Part 2: cause of death misclassification and the recent rise and fall in prostate cancer mortality. *J Natl Cancer Inst* 1999; **91:** 1025–32.

65 Etzioni R, Legler JM, Feuer EJ, et al. Cancer surveillance series: interpreting trends in prostate cancer. Part 3: quantifying the link between population PSA testing and recent declines in prostate cancer mortality. *J Natl Cancer Inst* 1999; **91:** 1033–39.

66 Slevin TJ, Donelly N, Clarkson JP, English DR, Ward JE. Prostate cancer testing: behaviour, motivation and attitudes among western Australian men. *Med J Aust* 1999; **171:** 185–88.

67 Smith DP, Armstrong BK. Prostate-specific antigen testing in Australia and association with prostate cancer incidence in New South Wales. *Med J Aust* 1998; **169:** 17–20.

68 Perron L, Moore L, Bairati I, Bernard P-M, Meyer F. PSA screening and prostate cancer mortality. *Can Med Assoc J* 2002; **166:** 586–91.

69 Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ* 2002; **325:** 740.

70 Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998; **316:** 140–44.

71 American Urological Society. Executive Committee Report. Baltimore: American Urological Association, 1992.

72 Ferrini R, Woolf SH. Screening for prostate cancer in American men. American College of Preventive Medicine Practice Policy Statement. American Cancer Society Prostate Cancer Screening Guideline Conference 2000 Update, May 4–6, 2000. Atlanta, 2000.

73 Donovan JL, Frankel SJ, Neal DE, Hamdy FC. Screening for prostate cancer in the UK. *BMJ* 2001; **323:** 763–64.

74 American Medical Association. AMA Report 9 of the Council on Scientific Affairs. Screening and early detection of prostate cancer. CSA Report 9-a-00. 2000: 1–22.

75 American College of Physicians. Clinical guidelines: Part III. Screening for prostate cancer. *Ann Intern Med* 1997; **126:** 480–84.

76 Pope A. Essay on man. Epistle i.

77 Davey Smith G, Ebrahim S, Frankel S. How policy informs the evidence. *BMJ* 2001; **322:** 184–85.

78 Fossa SD, Eri LM, Skovlund E, Tveter K, Vatten L. No randomised trial of prostate-cancer screening in Norway. *Lancet Oncol* 2001; **2:** 741–45.

79 Davey Smith G, Sheldon TA. Innocent until proven guilty: reflections on the career of clofibrate. *J Epidemiol Community Health* 1993; **47:** 403–04.

80 Parkinson MC, Bott SRJ, Montironi R, Melia J. Screening for prostatic cancer and its evolution within Britain. *J Pathol* 2002; **197:** 139–42.

81 Bonneux L. Screening populations at low risk carries high risks. *BMJ* 2003; **326:** 53.

82 Selley S, Donovan J, Faulkner A, Coast J, Gillatt D. Diagnosis, management and screening of early localised prostate cancer. NHS R&D HTA Programme. *Health Tech Assess* 1997; **1:** 1–156.