



Should mass screening for prostate cancer be introduced at the national level?

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ABSTRACT

This is a Health Evidence Network (HEN) synthesis report whether or not to introduce mass screening for prostate cancer the national level. Prostate cancer is a major cause of death among men, with over 56,000 deaths in the European Union in 1998. There are no obvious preventive strategies, therefore screening has been considered to reduce the number of deaths. Opportunistic screening is widely carried out but there are no known national programmes to screen for prostate cancer.

Mass screening should not be introduced at the national level, unless supportive evidence is available from the ongoing screening or treatment trials.

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Summary

The issue

Prostate cancer is a major cause of death among men, with over 56,000 deaths in the European Union in 1998. There are no obvious preventive strategies, therefore screening has been considered to reduce the number of deaths. Opportunistic screening is widely carried out but there are no known national programmes to screen for prostate cancer.

Findings

There are no completed randomized screening trials, although two are underway. Evidence from non-randomized studies suggests possible benefit, but these results may not be reliable due to bias or alternative explanations. The main areas of uncertainty are the natural history of the disease, which appears relatively benign in many cases, and appropriate treatment for positive screened cases.

Policy considerations

Mass screening should not be introduced at the national level, unless supportive evidence is available from the ongoing screening or treatment trials.

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Introduction

Prostate cancer is a major cause of death among men in European countries, with nearly 145 000 cases and 56 000 deaths in the European Union in 1998. Rates of incidence vary considerably among countries (Table 1), and appear to be increasing because of more frequent and better diagnostic tests, an aging population and probably a true increase in incidence (1). There are no obvious strategies to prevent this disease, so screening has been considered as a possible intervention to reduce the number of deaths.

“Screening” means applying a test to a defined group of persons in order to identify an early stage, a preliminary stage, a risk factor or a combination of risk factors of a disease. It is a question of detecting phenomena that can be identified prior to the development of the disease. The object of a screening service is to identify a certain disease or risk factor for a disease before the affected person spontaneously seeks treatment, in order to cure the disease or prevent or delay its progression or onset by early intervention (2).

Two tests are available to screen for prostate cancer: prostate-specific antigen (PSA) and digital rectal examination (DRE). The first of these is a blood test, and the second is a physical examination by a doctor where a finger is passed into the rectum to directly feel for enlargement or a nodule in the prostate gland. The subsequent diagnostic test is a prostatic biopsy taken through the rectum. This paper will discuss the use of PSA as part of a screening program. In clinical practice DRE is used to supplement rather than replace PSA.

Wilson and Jungner described a set of criteria against which a decision to implement a population screening program could be taken (3). These have since been considered and updated by, among others, the Council of Europe (2), which recommended those criteria listed in the box. These provide a standard against which we have assessed a policy of introducing mass-screening for prostate cancer at the national level.

Criteria for selecting diseases suitable for screening (Council of Europe 1994)

1. The disease should be an obvious burden for the individual and/or the community in terms of death, suffering, economic or social costs.
2. The natural course of the disease should be well-known and the disease should go through an initial latent stage or be determined by risk factors, which can be detected by appropriate tests. An appropriate test is highly sensitive and specific for the disease as well as being acceptable to the person screened.
3. Adequate treatment or other intervention possibilities are indispensable. Adequacy is determined both by proven medical effect and ethical and legal acceptability.
4. Screening followed by diagnosis and intervention in an early stage of the disease should provide a better prognosis than intervention after spontaneously sought treatment.

Sources for this review

We searched the Cochrane library and the INAHTA database, seeking systematic reviews on the effectiveness of screening for prostate cancer. We also searched the AHRQ web site and obtained the WHO guidance on screening for prostate cancer using their web site.

Findings from research and other evidence

We found three recent systematic reviews or health technology assessment (HTA) reports of screening for prostate cancer (4, 5, 6) We also found an HTA review from 1999, which summarized the evidence from eight previous reviews (1).

1. Burden of disease

Prostate cancer ranks second after lung cancer in male cancer deaths. The data for countries of the European Union is shown in Table 1. The number of deaths would satisfy the first of the criteria for introducing a screening programme, burden of disease.

Table 1 Incidence and death rates from prostate cancer by country in 1998

Population	Cases	Age-standardized rate (per 100 000)	Deaths	Age-standardized rate (per 100 000)
European Union	144 504	67.55	56 035	25.55
Austria	3667	89.49	1139	27.21
Belgium	5566	95.34	1846	30.59
Denmark	1627	53.89	1009	32.11
Finland	3087	121.84	777	31.02
France	28 135	87.10	9239	27.08
Germany	30 911	77.21	11 417	26.65
Greece	2823	41.00	1208	17.22
Ireland	1138	69.57	514	30.68
Italy	19 258	52.78	7109	19.12
Luxembourg	163	78.53	49	24.42
The Netherlands	6594	85.74	2383	30.25
Portugal	3210	55.23	1653	27.92
Spain	10 659	45.33	5742	23.76
Sweden	6610	114.95	2480	37.71
United Kingdom	21 056	60.97	9470	26.41

Source: EUCAN database

2. The natural history of the disease and the screening tests

The natural history of prostate cancer is not fully established. There is a spectrum of duration and severity. It is slow-growing in many cases and has a long phase in which it remains undiscovered. This

long latent phase is potentially advantageous for screening, but it appears that some tumours are very slow-growing and may never become clinically important (7). Men with these tumours often die from another cause (8). The mortality in men with very localized tumours is little different from that of other men (9). The relatively benign course of many tumours means that treatment might not benefit – and could harm – the men concerned.

There are in principle two tests that may be used in mass screening, PSA (prostate specific antigen) and DRE (digital rectal examination). The PSA test is simple, cheap, safe and acceptable. However the prostatic biopsy, required to investigate positive results, is less acceptable and carries significant risks. The accuracy (sensitivity and specificity) of the PSA test is difficult to determine (4). There is no good standard against which to test it, since prostatic biopsy may itself miss 10% to 30% of cases. Also, biopsies are not normally done on men with a negative PSA, so it is difficult to assess the number of false negative tests and measure sensitivity of the PSA test. Testing does not differentiate between the relatively harmless tumours and those that are likely to be fatal; therefore it is not specific for clinically important disease. Digital examination is less acceptable and less accurate than PSA testing (4).

3. Diagnosis and treatment

Facilities to investigate and treat men with an abnormal screening result are required for a mass program to be introduced. Many countries do not have sufficient capacity. The treatments available for localized prostate cancer such as that found at screening are: radical prostatectomy (surgery), radiotherapy and “watchful waiting.” In this third case (also known as “active monitoring”) men are followed up and only treated if there is evidence of disease progression.

There is evidence from one trial that radical surgery may reduce prostate cancer deaths compared to watchful waiting. There was no difference in overall mortality between the groups, although the mean follow-up of six years may be too short to exclude an effect (10). There is no evidence from randomized controlled trials that radiotherapy is better than watchful waiting (4). This is also true of external beam radiotherapy or brachytherapy, the insertion of radioactive seeds into the prostate gland.

The outlook for men with localized prostate cancer can be excellent, and watchful waiting can produce survival rates similar to those of more aggressive treatment (9, 10, 11, 12, 13, 14). Screen-detected cancers are mostly of this type.

Treatment, however, can cause harm as well as benefit. The principal adverse events of surgery are sexual dysfunction and incontinence. Surgery can be fatal in 0.1% to 0.3% of cases. Radiotherapy can cause sexual dysfunction, urinary symptoms and diarrhoea or rectal bleeding (See Table 2).

Furthermore there are important potential harms at a population level. These can arise from the diversion of healthcare resources from other more effective treatments into an ineffective or poorly performing screening program.

Table 2 Risk of complications following surgery or radiotherapy.(5)

Risk	Surgery (%)	Radiotherapy (%)
Death	0.1 – 0.3%	<1
Erectile dysfunction 2 years post-op	79.6*	6.5
Incontinence	9.6	3.5

*The rate may be as low as 32% with bilateral nerve sparing surgery by experts. It is not known whether this rate can be generally achieved.

4. Improvement of prognosis by screening rather than spontaneous presentation.

This criterion requires that the overall screening program be effective. It is one that can only truly be answered by randomized controlled trials (RCTs). Comparing mortality in non-randomized studies can be biased by a tendency for screening to find slower-growing tumours, which have a better survival rate. The RCTs should measure total mortality in order to show whether a program actually improves survival or just provides diagnosis earlier in the course of the illness. One RCT of PSA and digital

examination is reported (15), but the design is complicated and it may not be a true RCT (5). The result suggests that there was no difference between the screened and unscreened groups (4, 5).

Ecological studies are less satisfactory for assessing the effectiveness of screening. These studies compared the mortality from prostate cancer in populations in different locations or at different times, where the use of screening had changed, giving a mixed picture (4). There appears to have been a drop in mortality after the introduction of PSA testing in North America, but this drop came sooner than expected, and may be due to better treatment rather than screening. Furthermore, comparison of different areas with different intensities of testing gives conflicting results. A fall in mortality also appeared in the Austrian Tyrol compared to other parts of Austria that did not introduce screening (16). This could be the effect of screening or could be due to better treatment. Taken together, no firm conclusions can be drawn from the ecological studies.

It remains unclear whether mass screening does actually improve prognosis compared to spontaneous presentation. The areas of doubt are caused by the harmless nature of some tumours (and hence the likelihood of relative harm arising from treatment), and the uncertainty over the best treatment for screen-detected cancer.

Discussion on the strength of the evidence

There is no evidence yet from RCTs to support the introduction of mass screening. There is some population-level evidence in support of screening, but it is unreliable, since the findings may be due to better treatment, for example. The evidence suggests that only the first of the four Council of Europe criteria is satisfied.

Discussion of other aspects

- No public health technology assessment program has supported prostate cancer screening. There are no formal population screening programmes in Europe or North America (17). Nevertheless, the survey of institutes in International Network of Agencies for Health Technology Assessment (INAHTA) found that there was significant opportunistic screening activity taking place in most member countries, either as part of research or at the discretion of individual clinicians. The lack of formal programmes reflects partly an acknowledgement of the evidence (for instance in the United Kingdom and United States) and partly the relative fragmentation of preventive health services in some countries, where other screening services are also not established.
- Costs: It was estimated that in Canada in 1995 it would cost \$121 per man screened in the first year, or \$317 million total. This emphasizes the potential harm to other people that could be done by diverting resources away from other (effective) technologies.
- Ongoing projects: There are two major randomized controlled trials of screening underway. The European Study for Screening of Prostate Cancer (ERSPC) was planned to recruit 190 000 men (18). The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) completed recruitment of over 150 000 participants in 2001 and will follow them for up to 14 years (19). The size of each trial is set to detect a difference of 20% in mortality after 10 years, thereby determining whether screening can reduce deaths by this extent. There is a collaboration between the trials and both could produce very good evidence about whether screening is effective. One potential barrier to providing that evidence is the amount of opportunistic screening activity among the control group. This will reduce the trials' ability to detect benefit from screening.

There are also trials underway evaluating curative treatment in screen-positive men. An example is the ProtecT study funded by the HTA Programme in England, which compares radical prostatectomy, radiotherapy and watchful waiting/ active monitoring (20).

Current debate and the involved stakeholders

Prostate cancer screening is controversial. On the one hand health technology assessment and public health groups generally do not advise mass screening, whereas some specialist groups and patients advocate it, for example:

- The World Health Organization advises that: “It is necessary to establish the effectiveness of screening programmes for prostate cancer by performing well-designed randomized trials, before making any recommendation for public health policy” (International Prostate Screening Trial Evaluation Group, 1999).
- The United States Preventive Services Task Force (USPSTF) concludes that “the evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate specific antigen (PSA) testing or digital rectal examination (DRE)” (21).
- The Advisory Committee on Cancer Prevention in the European Union recommends that “As long as randomized studies have not shown an advantage on prostate cancer mortality or related quality of life, screening for prostate cancer is not recommended as a health care policy” (22).
- By contrast the American Urological Association reports that “most experts agree that healthy men over the age of 50 should consider prostate cancer screening with a DRE and PSA test” (23).
- The American Cancer Society (ACS) recommends that “the prostate-specific antigen test (PSA) and digital rectal examination (DRE) should be offered annually beginning at age 50 to men who have a life expectancy of at least 10 years” (24).

In the light of these confused recommendations men have found it difficult to have confidence in expert advisors. Because other (women's) cancer screening programs are effective and supported by government agencies, there is disbelief that prostate cancer screening is an exception. Men who have screened positive for prostate cancer believe that their lives have been saved by the programme (25). Consumer groups, particularly in the United States, lobby for the wider availability of screening (26). Men wish to participate actively in decisions about their health on the basis of full information, including PSA levels (27), and professional organizations support this attitude (28). Men find it unacceptable to have this information denied. They judge in some cases that the scientific argument hides the real reason for not introducing the service: underlying lack of resources (29). In the presence of these competing views, opportunistic PSA testing by clinicians is widely practiced, for instance in Germany (30), Greece (31) and Italy (32).

In summary, there are two camps in the debate. On the one hand are the public health specialists who argue from epidemiological principles that there is severe doubt about whether a mass screening program would be effective in the population. They suggest that it may possibly do more harm than good. On the other hand are individuals and professional organizations who argue that men have the right to know vital information that could save their lives. This is a question of population benefits or harms versus individuals' right to choose. But it is also a question of incomplete information being available to the men, who may not understand the possible harms that screening may cause them.

Conclusions

Studies in different populations do not provide good evidence that mass screening for prostate cancer does more good than harm. Two large screening trials are underway and may provide this evidence. Further treatment trials are also underway and will help policy makers.

Policy considerations

Until the evidence concerning effectiveness emerges, national policy makers should not support mass-screening programmes. There needs to be some control of the opportunistic testing currently being carried out. Aside from not supporting national screening, the United Kingdom and United States have advocated informing clinicians of the uncertainty surrounding the technology and fully informing men of the testing's implications (21, 33, 34). This policy may reduce the number of men tested and ensure that those proceeding have given fully informed consent. This seems an appropriate response to the large number of tests being carried out despite the current screening policies, and is recommended.

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