Screening for prostate cancer

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Epidemiological background

Prostate cancer is recognised as a major problem in general healthcare and specifically in the field of care for cancer. According to the most recent Globocan data referring to the year 2008, 903,000 men worldwide were diagnosed, and 258,000 died of prostate cancer. In spite of these impressive figures and in spite of the fact that in many Western countries prostate cancer is now the number one cause of cancer death in men, the overall risk of death in comparison to all other causes of death in men is relatively low. The lifetime risk of death from prostate cancer amounts to 2.5–3% in most Western countries. Dramatic differences are seen if these data are compared with those for Asian countries and some southern European and Mediterranean areas.

The figures and differences referred to in this section are summarised in Table 1. In spite of recent progress in early diagnosis, early aggressive treatments and treatment of more advanced disease, up to 14-fold differences in mortality still remain between countries with low and high mortality rates [1]. Incidence rates are strongly influenced by the use of prostate-specific antigen (PSA) for early diagnosis. The strong variation of PSA testing between individual countries confuses the value of the incidence data and leads to large differences in the incidence–mortality ratios.

Important changes over time in prostate cancer mortality have occurred in various regions of the world. A very large decrease in prostate cancer mortality has been witnessed since 1993 in the United States, which is an average of almost 4% per year. This resulted in a 30% decrease in prostate cancer mortality in the year 2000. Etzioni and colleagues [2] studied the reasons for this decrease in two modelling experiments and estimated that 45–70% of the change in mortality was because of screening. This in spite of the fact that screening in the USA only started in around 1991, and our knowledge of the lead time produced by screening, which ranges between 5 and 11 years [3,4]. In Europe similar but less pronounced decreases in mortality have been seen and described in longitudinal studies, using join-point regression analysis [5,6]. The data show no change in mortality in some countries (e.g., Belgium, Denmark) and a rather pronounced change in other countries such as Finland, France, Switzerland and the Netherlands. The reasons for these decreases in mortality remain largely unclear at the moment. While it is likely that some of this change is because of widespread screening in some countries, other factors, which in part precede the introduction of screening, such as the increased use of radical prostatectomy and high-quality radiotherapy in conjunction with endocrine treatment, which already started in the 1980s, have probably contributed. More recent information suggests that the use of statins in about 25% of the US male population may have contributed [7]. Intercurrent deaths due to other non-prostate cancer-related causes and prostate cancer mortality are competing events in an ageing male population. Men with prostate cancer die at an average age of 75 to 80 years [1]. An individual man, but also a population of men with an increasing life expectancy is at higher risk of dying of prostate cancer. In the Netherlands during the next 30 years it is expected that the population of males ageing to 65 years or older will increase from the current 15 to 26%. This is in part due to increasing life expectancy, but also due to the 'baby boom' observed right after the Second World War. It has been estimates that this will lead to an increase in new cases diagnosed up to the year of 2035 of at least 51% and an increase from 2,050 to 5,855 prostate cancer deaths. Clearly, efforts to decrease prostate cancer mortality, and specifically statistics reporting changes, in the future will have to take into account these important trends.

The slow natural history and the large differences in prostate cancer mortality in different regions of the world suggest that early diagnosis and early treatment, as well as preventive measures, should be successful. Randomised screening studies, which will be dealt within the next section, indeed indicate that systematic screening decreases prostate cancer mortality at a population and personal level. Unfortunately, the probably lifestyle-related differences in prostate cancer

Table 1
Incidence and mortality of prostate cancer in different areas of the world [1]

	Incidence		Mortality		Rate Ratio Incidence/Mortality 2008
	Cases (N)	Crude rate	Deaths (N)	Crude rate	
World	903,000	26.5	258,000	7.6	3.6
East Asia	83,000	10.2	27,000	3.3	3.1
South-East Asia	29,000	3.6	20,000	2.2	1.6
Europe	383,000	89.1	94,000	21.9	4.1
Southern Europe	80,000	106.6	20,000	27.4	4.0
USA	186,000	121.2	28,000	18.6	6.5

mortality between eastern and western countries have still been insufficiently explored and have not led to the introduction of effective, preventive treatments.

Historical background

Since a better understanding of the slow natural history of prostate cancer became available through observational studies in the 1970s and 1980s the concept that screening might prevent clinical progression and death from prostate cancer gained ground. Urologists and epidemiologists have learned to differentiate between a pre-clinical detectable phase and a phase during which some prostate cancers might progress and eventually lead to symptoms and death. Knowledge gained from the Baltimore Longitudinal Study of Ageing (BLSA) was crucial [8] and together with a study of the natural history of locally confined disease conducted in the Connecticut region in the United States significantly promoted our understanding of the natural history [9]. In the BLSA a large cohort of men were followed clinically and with periodic determinations of PSA levels. This allowed a comparison of control subjects without prostatic pathology, BPH participants, patients with loco-regional prostate cancer, and those patients who developed metastases and/or died of their disease. The key message is that for a period of 8–10 years those who develop progressive disease had slightly elevated PSA levels, but the slope of PSA progression was similar to all three control groups. This is the basis for the later observation that in a screening setting where the pre-clinical detectable phase utilised is the speed of rise, expressed as PSA velocity or PSA doubling time, did not correlate with the diagnosis of prostate cancer [9,10]. Albertsen and colleagues [11] identified 767 men with localised prostate cancer who were all conservatively managed between 1971 and 1984. His study allowed the proportion of men who died of prostate cancer out of all 767 and those who died from other causes to be identified. This for the first time identified a group of men with low prostate cancer aggressiveness (Gleason score <6), who had an extremely favourable prognosis over 15–20 years [12].

Even before such information became available Kimbrough, an urologist working for the US army, promoted rectal examination for the early diagnosis of prostate cancer [13]. Based on his findings the first early detection programme was introduced by Alken in Germany in 1961. This action was later taken over by the German government as the first preventive programme in prostate cancer ('*die Vorsorge Untersuchung*'). Several subsequent attempts were made to evaluate this programme, but it was never possible to show an effect on a population level. Still, the programme is still in place, but prostate-specific antigen (PSA) has not been added as a screening test. Similar programmes have never been formalised in any other country. With increasing knowledge that screening for prostate cancer decreases prostate cancer mortality at the cost of considerable losses in quality of life some countries, initially the UK, have introduced policies that impose the need for balanced information on one side and permit paid early detection measures for those who still wish to undergo screening [14].

Description of screening tools and their diagnostic performance

The diagnostic values of the presently available screening tools rectal examination (DRE), prostate-specific antigen, and ultrasound imaging of the prostate (TRUS) have all been extensively evaluated and were subject to recent comprehensive reviews. DRE and TRUS in a screening setting have most recently been evaluated in [15–17]. Comparisons are made with PSA as the only screening test. The added value of DRE to PSA-alone techniques is very low. A small increment of detection of aggressive cases by DRE is

Table 2
Performance characteristics of PSA [9]

PSA level	Any PCa vs. no PCa		Gleason ⩾7 vs. <7 or no PCa	
	True positive (%)	True negative (%)	True positive (%)	True negative (%)
1.1	82.0	40.6	92.8	37.0
1.6	67.4	58.8	84.4	54.8
2.1	54.4	70.8	75.6	67.3
2.6	43.6	79.6	67.2	76.5
3.1	35.8	85.1	57.6	82.3
4.1	24.5	92.3	40.4	90.0
6.1	5.4	98.0	13.2	97.8
8.1	2.0	99.1	4.8	99.0
10.1	1.0	99.5	2.4	99.5

likely, but its added value in a randomised setting and with repeated screens has not been confirmed.

Prostate-specific antigen is the main screening test in current use for randomised trials and in opportunistic screening (screening upon request). The only study that allows a comparison of PSA as a screening test in relation to a control population has recently been published [18]. The study that uses historical controls from the Irish cancer registry in comparison with data derived from the European Randomized study of Screening for Prostate Cancer (ERSPC) evaluates the value of PSA at entry in relation to prostate cancer mortality and shows a strong correlation. No effect of screening is seen over a total follow-up period of 12 years for men who initially presented with PSA values below 3.99 ng/ml. Men with PSA values between 10 and 20 ng/ml showed the highest risk of prostate cancer death, but also the largest effect of screening. PSA values between 4 and 10 ng/ml were intermediate.

These data seem to support a cut-off value of 3–4 ng/ml for the early diagnosis of prostate cancer. The only available information that conclusively studies the performance characteristics of PSA, however, is derived from the Prostate Cancer Prevention Trial (PCPT). In a setting where more than 8,000 men with initial PSA values less than 3.0 ng/ml were biopsied seven years after having participated in the placebo group of this study, showed that there is a continuous relation among prostate cancer detection, aggressiveness of prostate cancers by Gleason score, and PSA values. A cut-off point with similar sensitivity and specificity cannot be identified [19]. The data are shown in Table 2. The clinical relevance of missing cancers and specifically high-grade cancers in the very low PSA ranges is at this moment unclear. Information from ERSPC Rotterdam, however, shows that the chance of having a positive biopsy for a man with a PSA value <1.0 ng/ml over an eight-year period is negligible [20]. The data also show that at commonly used cut-off points of detection the rate of true positives (sensitivity) and true negatives (specificity) is extremely low and variable. This is mainly due to the fact that PSA is not only produced in prostate cancer, but also in benign prostatic hyperplasia and at increasing serum levels in men who suffer from prostatitis.

It seems attractive to lower PSA cut-off levels to an age where the interfering disease entities, specifically benign prostatic hyperplasia (BPH), are infrequent or non-existent. It has been shown that in men aged 44–50 a PSA value of 1 ng/ml or higher was associated with an almost fourfold risk of a clinical diagnosis of prostate cancer 25 years later [21]. In the same cohort derived from the Malmö Healthcare Study it was shown that in men below the age of 60 a PSA concentration above the median of 1.0 ng/ml were at increased risk of developing metastatic prostate cancer. Conversely, the study suggests that men below the age of 60 with a PSA value of <1.0 ng/ml might be exempted from screening for a long period of time. Similar findings were obtained from the database of the BLSA where it was shown that the relative risk of prostate cancer in men aged 40–50 was 3.75 when PSA levels were >0.6 ng/ml, which was the median value in this population [22]. Early detection in young men below the age of 50 has been included in the recent guidelines of the National Comprehensive Cancer Network (NCCN) [23]. In this setting it remains unclear how younger men with an 'elevated' PSA should be followed further and under which circumstances a biopsy should be recommended. This issue should be subject to further research.

There are two main downsides of opportunistic, PSA-driven early diagnosis. One is the very low specificity necessitating unnecessary biopsies in 56–75% of cases. On the other hand, even with the very limited number of six lateralised biopsies as used in the ERSPC study, the rate of overdiagnosis has been determined to be around 50% [4]. Overdiagnosis in this setting is defined as the diagnosis of cancers that during the lifetime of their carrier will not cause any harm or lead to his death. These limitations will be further elucidated in the following sections.

Effectiveness of screening, evidence from randomised controlled trials

In spite of many limitations, which will be discussed later on, PSA still remains the most important test applied for the early detection of prostate cancer and also in the randomised screening studies, which recently reported initial results.

The European Randomized study of Screening for Prostate Cancer (ERSPC) is a multicentre randomised controlled trial comparing a group of men to whom PSA driven screening was offered with a group of men who were randomised to a control arm and who were supposed not to undergo screening. The study started in 1993 and eventually included eight European countries: Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, and Switzerland. The Dutch centre (Rotterdam) is in charge of the international coordination. The main endpoint of the study is prostate cancer mortality; however, secondary endpoints under study include morbidity, mainly metastatic disease, aspects of quality of life, the assessment of quality of life-adjusted life years and, eventually, a multicentre analysis of cost-effectiveness. Men in the age group of 50–74 were recruited. The power considerations have been published [24]. Early on a core age group of men aged 55–69 was determined as the age group to which all centres contribute. As was agreed in a published evaluation plan, three interim analyses and a first final analysis are to be conducted on the data up to 31 December 2008 and during every second year preceding this date. A total of 162,387 men were recruited to the core age group. The results, which are to be published during 2011, are also based on this core age group. The age groups of 50–54 and 70–74 are included in separate analyses. The screening interval amounted to four years in 87% of the population; Sweden used a two-year screening interval and recruited 13% of the study population. Indications for prostate cancer biopsy were driven by a PSA level of $\geqslant 3$ ng/ml. Ancillary testing occurred in some centres for various periods of time and included rectal examination, free total ratio of PSA in the PSA range 3–4, and a higher PSA cut-off during the initial phase of the study. The power calculation of the ERSPC study was based on the population that was in fact screened [25]. The study was estimated to have a power of 86% to show a 25% difference in prostate cancer mortality at a p value of 0.05 by 31 December 2008. The study was monitored by an independent data monitoring committee. Independent causes of death committees determined the causes of death according to an internationally accepted algorithm [26]. The three interim analyses were planned upfront. The power calculation was corrected for alpha spending. A total of 72,890 men were randomised to screening and 98,353 to the control group. The numerical difference results from the fact that the Finnish centre randomises at a ratio of 1:1.5 between screening and control. Further detailed information is available from the publication after nine years of follow-up, which is in fact based on the interim analysis after nine years. The significant difference shown at that time came as a surprise to the investigators and to the data monitoring committee [10]. At that time, based on the data up to 31 December 2006, positive tests were seen in 16.2% of the screened population, compliance with biopsy indication was 85.8%, and a total of 17,543 biopsies were carried out. The PPV amounted to 24.1%. 214 prostate cancer deaths occurred in 5,990 prostate cancers identified in the screening arm and 326 deaths were seen in 4,307 men in the control arm. At a median follow-up of nine years a 20% reduction in prostate cancer mortality in the intention to screen analysis was seen ($P = 0.04$). This mortality reduction was associated with a number needed to screen of 1,410 and a number needed to treat of 48 to save one prostate cancer death with respect to the control group.

A secondary analysis was conducted that adjusted for non-compliance in the screening arm and contamination by PSA use in the control arm [27]. These adjustments showed a net benefit for those men who in fact were screened of 31% in terms of reduction of prostate cancer mortality by screening.

The second large randomised trial, the Prostate, Lung, Colorectal and Ovary screening trial (PLCO), conducted by the National Cancer Institute of the United States, also reported in 2009 [28]. In this study 76,693 men were randomised in ten US centres between screening and 'usual care'. The trial was reported after seven years of follow-up at an interim analysis with an almost complete identification of

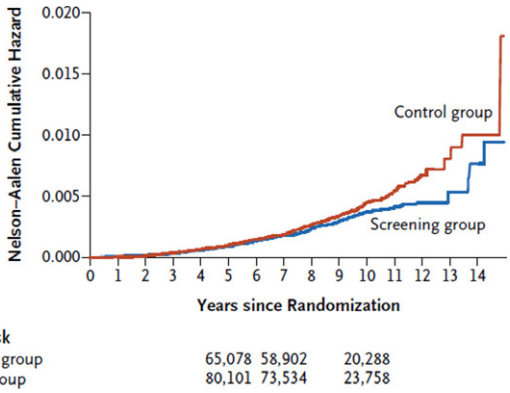

Fig. 1. Cumulative risk of death from prostate cancer (PC) from the European Randomized study of Screening for Prostate Cancer (ERSPC) [10].

prostate cancer mortality. Unlike the ERSPC study, this trial did not show a significant difference in prostate cancer mortality in favour of screening. It is felt that the results of the ERSPC and PLCO study are not contradictory. The differences are explained by a shorter average follow-up in PLCO, low rates of compliance with biopsy in the screen arm, which amount to only about 40%, a high rate of testing of 44% in men prior to randomisation, which likely decreased the number of potential endpoints in both arms, and a 53% contamination rate in the control arm. All this resulted in low rates of prostate cancer death in both arms and no difference in mortality.

The Gothenburg Randomized Screening Trial of prostate cancer became part of ERSPC in 1995. It was established and designed as an independent study in 1994. According to its own power calculation the study reported its data in 2010 [29]. Owing to legal regulations in Sweden, it was possible to identify 20,000 men aged 50–64 in the Gothenburg population registry and to randomise these without their knowing about it, between screening and control during 1994. This resulted, in line with the power calculation of this trial, in a 14-year follow-up on the basis of the mortality data up to the end of 2008. With a 14-year follow-up the trial showed a relative reduction of 44% of prostate cancer mortality ($P = 0.002$) in favour of screening in the intention to screen analysis. After adjustment for non-participation, the relative reduction of prostate cancer mortality amounted to 56%. These data were associated with a number needed to screen of 293 and a number needed to treat of 12. Taking into consideration the trend seen in the mortality curves of the ERSPC study as whole (Fig. 1) it may be expected that similar results could be confirmed in the multicentre setting of this study with longer follow-up.

Overdiagnosis and overtreatment

Overdiagnosis is defined as the diagnosis of cases that will not harm during lifetime and will not kill their carrier. Overdiagnosis depends on two factors: the aggressiveness of a given tumour and the life expectancy of a given patient. Overdiagnosis has been estimated to be in the range of 60–93% [30] and up to 35% with a follow-up period of seven years [31]. Overdiagnosis and the resulting overtreatment are considered the main reason why population based screening for prostate cancer is at this moment unacceptable [10]. The best way to prevent overdiagnosis would be the development of a marker substance or an imaging technology that might allow prostate biopsy to be avoided in cases with potentially non-aggressive cancers of which the histology and rate of progression would be similar or identical to the very prevalent cancers found at autopsy or in prostate specimens removed for other reasons. Unfortunately, such a marker substance is not available and does not seem to be becoming available in the near future. However, patient-related or clinically available risk modifiers, which can be used in risk calculators to alter the biopsy indication driven by PSA alone, are available. In a risk calculator based on outcomes in men participating in the ERSPC study Rotterdam PSA, prostatic volume, a normal or abnormal rectal examination, and ultrasound study were identified as independent predictors [32]. Level 3 of this risk calculator [33] can be used to modify the risk of a positive biopsy. A man with PSA of 4.0 ng/nl in this study has a risk of a positive biopsy of 21%. If the risk cut-off were lowered to 12.5% and the additional risk modifiers were applied while using risk calculator 3 this would result in 33% fewer biopsies, an increase in the PPV from 21 to 33% and the diagnosis of 14% fewer prostate cancers. In this setting 139% of all cases included in the analysis were progressive and only 15 of the progressive cases would be missed. All prostate cancer patients who died over the study period of nine years were identified by the use of the 12.5% cut-off. Other options for probability cut-off values are given in Cavadas and colleagues [33]. The use of the risk calculator to modify the number of biopsies and to decrease the number of non-aggressive prostate cancers diagnosed is recommended above using PSA alone. The SWOP/ERSPC risk calculator [32] has been recently found in an independent analysis to be superior to the PCPT trial-based NCI risk calculator, which does not include one of the main predictors: prostate volume [33].

One other option may become part of daily clinical application in the future: the use of multi-parametric

MRI studies. It seems possible with this technology to selectively identify aggressive disease and to avoid biopsies in about 50% of suspicious lesions, which would otherwise be identified as indolent cancers. Efforts are underway to study the value of MRI in screening for prostate cancer in a prospective, randomised study in cooperation with the ERSPC Rotterdam study group and the MRI centre in Nijmegen, the Netherlands. Expertise developed there has been the subject of several publications including Sciarra and colleagues and Hambrock and colleagues [34,35]. In spite of the lack of a large cooperative study producing convincing evidence and in spite of the lack of a randomised comparison with standard biopsy techniques, the use of MRI to identify aggressive prostate cancers specifically located in the ventral region of the prostate is increasing.

Should PSA-based screening become a healthcare policy?

The answer of the ERSPC study group as phrased in Schröder and colleagues [10] is a clear 'no'. The main reason is the high level of overdiagnosis of about 50% that is seen with PSA-driven screening. Even in the setting of the Swedish study in which we see much more favourable numbers needed to screen and numbers needed to treat in order to save one prostate cancer death the issue of overdiagnosis and potential overtreatment of >50% remains [4]. On the other hand, the significant mortality reductions seen with nine-year and longer follow-up periods and the higher level of mortality reduction seen in men who are in fact undergoing screening (as opposed to the population of men as a whole) suggests that PSA-driven screening should have a place in clinical practice as well as possibly in healthcare policy. However, it will be necessary to find mechanisms to decrease overdiagnosis defined as the diagnosis of cancers that otherwise would never surface during a man's lifetime. Unfortunately, marker substances that are under development do not seem to be sufficiently promising to replace PSA [36–38]. At present, the application of additional risk factors included in risk calculators seem to be a more effective option [39]. Applying the ERSPC/SWOP risk calculator (www.prostatecancer-riskcalculator.com) to a man with a PSA of 4 and favourable or unfavourable outcomes of rectal examination, prostate volume determination or abnormalities on transrectal ultrasound result in a chance of 8% or 65% of a positive biopsy for the same PSA level.

What is the future of prostate cancer screening?

Prostate cancer screening may turn out in the end to be more effective in terms of lowering prostate cancer mortality than other forms of screening applied to other cancers that are already part of healthcare policies, such as breast, cervix, and colon cancer. However, the follow-up in the ERSPC study and certainly in the PLCO study is too short to show the full value of screening. Also, screening algorithms need to be elaborated further to avoid overdiagnosis as the biggest adverse effect of screening. Quality of life adjustment of screening results will have to show a positive balance. Also, cost-effectiveness is still under study. Considering these factors, it seems premature to propose the introduction of screening as a healthcare policy. However, the available results should introduce major changes in decision-making in clinical practice and also on healthcare policies. As far as clinical practice is concerned, appropriate, balanced and validated information to men who wish to be screened is mandatory. Only after having taken note of such information should PSA-driven diagnosis be applied to an individual man. However, in this situation it should also not be refused. At the level of general healthcare, the time has come to recommend pilot studies evaluating aspects of screening that would be relevant for the given healthcare systems provided the introduction of screening for prostate cancer becomes advisable through progressing evidence. Finally, it would be desirable for men to be able to benefit from preventive efforts that are already in clinical practice in women.

Conflict of interest statement

The author has no conflicts of interest to declare.

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