

Prostate Cancer Screening with PSA

A Study of Potential Negative Consequences

Doctoral Thesis

by

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Front cover: *Gulls reflecting upon PSA screening*

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“At the heart of the screening debate lies the ethics of information.”

Ian S Markham. *British Medical Bulletin*.
1998; 54(4): p.1012.

To My Family

Abstract

Prostate Cancer Screening with PSA – A Study of Potential Negative Consequences

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Aims: The Göteborg randomized population-based prostate cancer screening trial is a prospective study evaluating the efficacy of prostate-specific antigen (PSA)-based screening and its effect on prostate cancer mortality. The potential negative consequences in relation to benefits for men undergoing this screening are explored in this thesis.

Methods: As of December 31, 1994, there were 32,298 men born between Jan 1, 1930 and Dec 1, 1944 (ages 50-64, median 56 years) living in the city of Göteborg. Of these, 20,000 men were randomly allocated in a 1:1 ratio to either a screening group or to a control group. This population constitutes the basis for this thesis. The cumulative incidence of prostate cancer and prostate cancer mortality were calculated and analyses made by intention-to-screen. Anxiety levels were assessed in screen-positive men. Short-term overall mortality after prostate biopsy was studied. Perioperative mortality after radical prostatectomy was evaluated from registry linkage with the follow-up study of the National Prostate Cancer Register (NPCR) 1997-2002. Side-effects from radical prostatectomy were evaluated for men in the screening study who underwent radical prostatectomy at Sahlgrenska University Hospital between 2001-2008.

Results: A PSA-based screening program reduced the relative risk of prostate cancer mortality by 44% over 14 years. Overall, 293 men needed to be invited for screening and 12 to be diagnosed to prevent one prostate cancer death. Attending a screening program for prostate cancer is seldom associated with severe negative psychological distress, even for men with persistently elevated PSA levels. The risk of excess fatal complications after biopsy of the prostate is low. Radical prostatectomy is a procedure with very low perioperative mortality throughout the whole of Sweden. With 14 years of screening, for each prostate cancer death averted, the surgically induced morbidity due to screen-detected prostate cancer will render four men impotent or sexually inactive, and less than one man incontinent.

Conclusions: PSA screening significantly, and substantially, reduces prostate cancer mortality. This benefit compares favorably to other cancer screening programs. The potential negative consequences of such screening may be acceptable in the light of a disease-specific mortality reduction. The risks of severe consequences from the screening procedures and radical prostatectomy seem minor, but the risk of negatively influencing the sexual performance may be substantial. The outcome on a population level may differ from the benefit for the individual.

Keywords: prostate cancer; screening; mortality; early detection; anxiety; 30-day mortality; prostatectomy; Prostate-Specific Antigen; prostate biopsy; impotence; urinary incontinence

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Jonas Hugosson, **Sigrid Carlsson**, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg and Hans Lilja. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol.* 2010 Aug; 11(8): 725-32.

II. **Sigrid Carlsson**, Gunnar Aus, Catrin Wessman and Jonas Hugosson. Anxiety associated with prostate cancer screening with special reference to men with a positive screening test (elevated PSA) – Results from a prospective, population-based, randomised study. *Eur J Cancer.* 2007 Sep; 43(14): 2109-16.

III. **Sigrid Carlsson**, Erik Holmberg, Sue M. Moss, Monique J. Roobol, Fritz H. Schröder, Teuvo L. J. Tammela, Gunnar Aus, Anssi P. Auvinen and Jonas Hugosson. No excess mortality after prostate biopsy – Results from the European Randomized Study of Screening for Prostate Cancer. *BJU Int.* 2010; *In press.* (doi: 10.1111/j.1464-410X.2010.09712.x.)

IV. **Sigrid Carlsson**, Jan Adolfsson, Ola Bratt, Jan-Erik Johansson, Christer Ahlstrand, Erik Holmberg, Pär Stattin and Jonas Hugosson. Nationwide population-based study on 30-day mortality after radical prostatectomy in Sweden. *Scand J Urol Nephrol.* 2009; 43(5): 350-6.

V. **Sigrid Carlsson**, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Johan Stranne and Jonas Hugosson. The excess burden of side-effects from treatment in men allocated to screening for prostate cancer. The Göteborg randomised population-based prostate cancer screening trial. Accepted for publication in *Eur J Cancer.* Oct 2010. (doi:10.1016/j.ejca.2010.10.016)

SHORT OVERVIEW OF PAPERS

Paper	Population and design	Endpoints	Main findings
I	<ul style="list-style-type: none"> The Göteborg randomized population-based prostate cancer screening trial Randomized controlled trial Population-based, prospective study (1995-2008) <p>n=10,000 screened n=10,000 controls</p>	<ul style="list-style-type: none"> Prostate cancer incidence Prostate cancer mortality Number needed to screen Number needed to treat 	<p>A PSA-based screening program increases the detection of prostate cancer by 1.6 but lowers the risk of advanced disease. This program also reduces the relative risk of prostate cancer mortality by 44% over 14 years.</p> <p>The number needed to screen to prevent one prostate cancer death is 293 and the number needed to diagnose is 12.</p>
II	<ul style="list-style-type: none"> The Göteborg randomized population-based prostate cancer screening trial Population-based, prospective and longitudinal study (1995-2005) <p>n=1,781 screen-positive men</p>	<ul style="list-style-type: none"> Anxiety awaiting the result of PSA measurement Anxiety associated with further clinical work-up including prostate biopsies 	<p>Anxiety associated with prostate cancer screening in general is low to moderate, even in men with elevated PSA.</p> <p>Severe anxiety affects a smaller group of susceptible men.</p>
III	<ul style="list-style-type: none"> Nationwide (Sweden) NPCR – National Prostate Cancer Register (the follow-up study) Localized prostate cancer (clinical stadium T1-2, Prostate-specific antigen < 20 ng/ml, men ≤70 years) (1997-2002) <p>n=3,700</p>	<ul style="list-style-type: none"> Perioperative (30-day) mortality after radical prostatectomy 	<p>Radical prostatectomy is a procedure with very low perioperative mortality throughout Sweden (0.11-0.13%), i.e. even when performed outside high-volume centers.</p>
IV	<ul style="list-style-type: none"> Sub-study within the European Randomized Study of Screening for Prostate Cancer, ERSPC Study centers: Finland, the Netherlands and Sweden Prospective cohort study (1993-2008) <p>n=12,959 screening-positive men n=37,235 screening-negative men</p>	<ul style="list-style-type: none"> 30,60,90,120- and 365 day mortality after screening (~biopsy) 	<p>Screening-positive men who are in fact biopsied have a lower short-term mortality as compared to screening-negative men.</p> <p>Prostate biopsy is not associated with excess mortality and fatal complications seem to be very rare in a screening setting.</p>
V	<ul style="list-style-type: none"> The Göteborg randomized population-based prostate cancer screening trial Men who underwent radical prostatectomy at Sahlgrenska University Hospital (sub-study) Population-based, prospective and longitudinal cohort study (2001-2008) <p>n=1,138 screened men with prostate cancer; 562 radical prostatectomies n= 711 controls with prostate cancer; 267 radical prostatectomies</p>	<p>Questionnaires preoperatively and 18 months after surgery:</p> <ul style="list-style-type: none"> - International Index of Erectile Function-5 - Urinary incontinence <p>n=205 screened men with complete questionnaires (72.4% of eligible men) n=89 controls with complete questionnaires (67.9% of eligible men)</p>	<p>At 18 months post radical prostatectomy, the majority of preoperatively potent men are impotent or sexually inactive, whereas 14.3% of screened men and 20.5% of controls are incontinent.</p> <p>However, at 14 years, the “cost” per prevented prostate cancer death is four men impotent and less than one man incontinent.</p>

Abbreviations and glossary

In alphabetical order and as they appear in the text:

AS	Active Surveillance
AUA	American Urological Association
BPH	Benign Prostatic Hyperplasia
CT	Computed Tomography
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
EAU	European Association of Urology
ED	Erectile Dysfunction
EPC	Early Prostate Cancer Trial
ERSPC	European Randomized Study of Screening for Prostate Cancer
F/T	Free to Total Ratio
GnRH	Gonadotropin-releasing hormone
HADS	Hospital Anxiety and Depression Scale
IIEF	International Index of Erectile Dysfunction
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NPCR	National Prostate Cancer Register
PAP	Prostatic Acid Phosphatase
PC	Prostate Cancer
PCPT	Prostate Cancer Prevention Trial
PDE5I	Prostaglandin 5 Inhibitors
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLCO	The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
ProtecT	Prostate testing for cancer and Treatment
PSA	Prostate-Specific Antigen
QoL	Quality of Life
QALY	Quality-Adjusted Life Years
RCT	Randomized Controlled Trial
RP	Radical Prostatectomy
SBU	Statens Beredning för medicinsk Utvärdering
SEER	Surveillance, Epidemiology and End Results program
SPCG	Scandinavian Prostate Cancer Group
START	Standard Treatment Against Restricted Treatment
TRUS	Trans-Rectal Ultra-Sound
TURP	Trans-Urethral Resection of the Prostate
UI	Urinary Incontinence
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization
WW	Watchful Waiting
5ARI	5-alfa reductase inhibitors

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1. INTRODUCTION

The present thesis investigates potential negative consequences in relation to benefits of a population-based, randomized, controlled prostate cancer screening trial conducted between 1995-2008 in Göteborg. Screening was performed every second year with the blood test Prostate-Specific Antigen (PSA) as a screening tool.

The first study outlined in this thesis reports the acceptability and efficacy of this prostate cancer screening program. It contains the first evaluation of the main endpoint at 14 years of follow-up, i.e. differences in prostate cancer mortality between 10,000 men randomized to screening and 10,000 controls. In the second paper, screened men's levels of anxiety associated with the screening procedures are assessed. The third paper explores the risk of excess mortality associated with prostate biopsy, the gold standard for the diagnosis. The fourth paper focuses on 30-day mortality after radical prostatectomy, the most common treatment option for early, screen-detected, localized prostate cancer. The fifth paper establishes the population-induced frequencies of erectile dysfunction and urinary incontinence after radical prostatectomy for men with screen-detected prostate cancers as compared to men with clinically diagnosed tumors.

1.1. Prostate cancer – the scope of the problem and epidemiology

Prostate cancer (hereafter referred to 'PC') is a worldwide health problem. It is one of the most prevalent cancer forms, especially in developed countries. The estimated incidence in the U.S. was 192,280 new cases in 2009¹ and 345,900 new cases in Europe in 2006²; accounting for 25% all newly diagnosed cancers in the U.S. and 20% in Europe. In Sweden, PC is the most common cancer in men; accounting for one third of new male cancer cases.³ It is now also the leading most common cancer, followed by breast cancer, cutaneous cancers and colorectal cancer.⁴ However, this has not always been the case.

History

Historically, the first genuine description of PC in the medical literature was given by Langstaff in the U.K. in 1817, based on the gross appearance at autopsy.⁵ The first PC case established by histological examination by an experienced microscopist was reported by Adams in 1853; stating that this was "a very rare disease".⁶ In the 1890's, only 50 to 67 PC cases were reported in the literature.⁷ This may have three explanations. Firstly, the main explanation for this may be that in the 19th century, the average life expectancy at birth was less than 50 years. Before 1940, most men did not live long enough to acquire the disease. Secondly, at that time, the distinction between benign disease and cancer causing obstructive urinary symptoms was poorly defined. However, some early histological studies of enlarged prostates and prostatectomy specimens revealed a 10-15% prevalence of PC.⁷ Thirdly, dietary habits and exposure to environmental carcinogens may have altered. As there exist large geographical variations in PC mortality (see below), suggesting environmental factors of importance, it may well be that PC is a "modern" disease.

Incidence

From being a barely recognized disease in the 19th century, the incidence of PC has increased dramatically during the last 100 years, with a rapid increase during the last two decades. A man's lifetime risk of a PC diagnosis has more than doubled, from 8% in the early 1980's to almost 18% today.⁸ This is due to a number of reasons. The introduction of the PSA (see below) is likely to explain most of this increase, reflected in the fact that the greatest increase in incidence constitutes of non-palpable tumors. Other reasons are believed to be an increased ageing male population with an increased life expectancy, an increased disease awareness (by men/patients and physicians), improved diagnostic techniques with more extended prostate biopsy schemes and also a true increase in incidence (due to dietary/ behavioral/ occupational effects).

The average annual increase in PC incidence in Sweden has been 2.7% over the last 20 years, with a decrease seen during the last years (2004 onwards).³ The incidence of PC in Sweden was around 2,500 new cases in 1970 increasing to around 6,500 in 1998, reaching a peak of nearly 10,000 new cases in 2004, now declining to around 8,700 in 2008.(Fig. 1)⁹

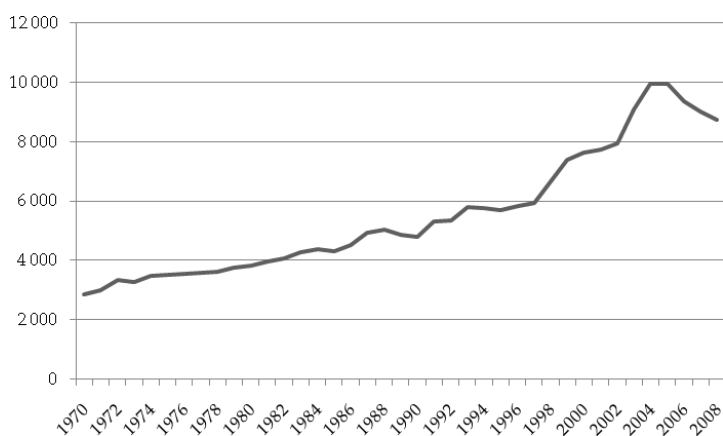


Figure 1. Prostate cancer incidence. Annual numbers of new prostate cancer cases diagnosed in Sweden 1970-2008. Graphical illustration: S Carlsson. Courtesy to Socialstyrelsen (National Board of Health and Welfare).⁴

Mortality

PC is the leading cause of cancer related death among Swedish men, followed by lung cancer and colorectal cancer deaths. In 2007, a total of 2,470 men died from the disease, of whom 311 men deceased before reaching 70 years.¹⁰ In Europe, according to estimates for 2006, PC was estimated to be the cause of death in 87,400 men, accounting for 9% of cancer deaths in men². The lifetime risk for a Swedish man today of dying from PC is around 5-6%; in 2007, 5.6% of 44,025 overall male deaths were due to PC, and 5.8% of 42,350 men aged 45 years or older⁴. This can be compared with cardiovascular/ circulatory diseases that in 2007 accounted for 40.7% of male deaths (all ages).⁴

The age-standardized mortality from PC in Sweden has slightly increased during the last two decades and the absolute number of deaths has increased.⁴(Fig. 2) Looking at the absolute number of men diagnosed with PC and the number of men who die from the disease each year in Sweden, it is evident that it is definitely not harmless.

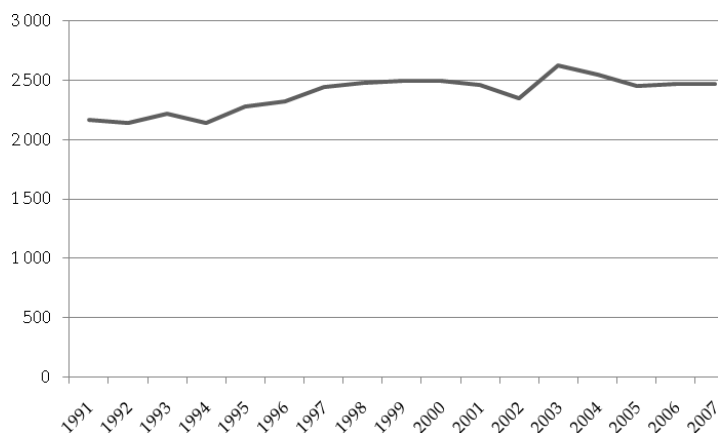


Figure 2. Prostate cancer mortality. Annual numbers of deaths from prostate cancer in Sweden 1991-2007. Graphical illustration: S Carlsson. Courtesy to Socialstyrelsen (National Board of Health and Welfare).⁴

Clinical presentation and natural history of the disease

Some decades ago, 25-30% of men with PC presented with metastasized disease with concomitant significant morbidity and mortality. In the early 80's, half the men with newly diagnosed PC had an incurable disease.¹¹ Before the PSA era, approximately 40% with the diagnosis died from the disease. At that time, the only strategy against PC was a digital rectal examination (DRE). However, the DRE as a screening tool found many tumors incurable by the time they were palpable.⁸ There was a call for another test that could detect tumors earlier (see below). Five years already after the introduction of PSA testing, most men had a curable disease¹². Today, we continue to see a decline in metastasized PC at diagnosis and the proportion of early tumors has increased.

The discrepancy between the risk of a PC diagnosis and the risk of dying from PC shows that, although some PCs cause suffering and death, others are clinically less important, i.e. they would never cause symptoms within the life span of a typical man and/or would never pose a threat to this man's life. This fact also highlights the importance of striving to develop new means of distinguishing those cancers that are destined to cause significant illness and premature death from those that are not.

In Sweden, most men are diagnosed with PC between 65 and 69 years,⁹ while most men who die from the disease are over 79 years⁴. The mean age at death from PC exceeds the life expectancy for a Swedish male, which has increased from around 71 years in 1960 to 79 years today¹³. This implies that many men will die from other co-

morbid conditions rather than PC¹⁴, i.e. they will “die with it, rather than from it”. But does this mean that “the old man’s disease” is not an important public health problem? The natural history of this disease is very heterogeneous. Frequently, the cancer progresses slowly and remains localized to the prostate gland. In other patients, tumor growth may be more rapid, resulting in cancer spreading beyond the confines of the prostate and long-term survival may be considerably diminished. Strategies for managing PC have therefore been aimed at detecting the tumors early. Patients who present with distant metastases in general have a poor prognosis with a median survival of 2.5 years, whereas men who have localized disease have a much better prognosis.¹⁵

A recent study has indicated, that if current life expectancy trends continue, more than half the babies born today in wealthy nations will live to 100 years.¹⁶ Reaching this age may seem unrealistic, however, data from Statistics Sweden estimates that the life expectancy at birth for a Swedish male will increase to at least 85 years by 2060.¹³ With an ageing population, the public health burden from PC will most probably increase.

1.2. Global incidence and mortality trends

The global incidence and mortality trends for PC are more complicated than for other tumors, and different explanations for the rises and falls seen over time and the geographically diverse patterns have been proposed⁸.

The trends before and during the PSA era constitute a historical shift in the detection and treatment of PC around the world. After its commercial introduction in the mid 80’s, the PSA test became widely used in the U.S. around 1990, both for diagnostic purposes in symptomatic men and as a screening test in asymptomatic men. PSA screening for men over 50 years was recommended by the American Cancer Society in 1992.¹⁷ From then on, epidemiological studies on population-based data originating from the U.S. so-called SEER-database (Surveillance, Epidemiology and End Results program) showed markedly altered incidence and mortality patterns.

Incidence trends

Firstly, there was an initial rapid and dramatic PC incidence trend peak that coincided with the widespread implementation of the PSA test in the late 80’s (1985-1992), but since the early 1990’s (1993 onwards) PC incidence has been declining. The initial increase was interpreted as being due to the depletion of previously undiagnosed accumulated cases from the previous years’ pool¹⁸ (a “harvest effect”). The detection of a large number of prevalent cases has also been suggested as being the first indication of a successful screening program in detecting the disease. During the 80’s there was also an increase in the use of transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH). Because of an increase in the pathological examination of TURP-specimens there was also an increasing likelihood of PC diagnosis.⁸

Mortality trends

The pattern of an initial increase followed by a decline was also seen in PC mortality from the early 90's and onwards. After a surge in PC incidence in North America in the early 1990's, diminishing rates of PC mortality became apparent in 1993.¹⁹⁻²⁰ The age-standardized mortality rates also declined in many countries worldwide²¹. In Tyrol in Austria where men, aged 45-74, have been offered PSA testing free of charge since 1993 within the Tyrol Prostate Cancer Demonstration Project (a non-randomized study of the effect of screening in a natural experiment setting)⁸ the decline in PC mortality has been much greater than in the rest of Austria²²⁻²³. However, there are some inconsistencies in PC mortality trends and the uptake of PSA screening worldwide, and not everywhere is there a correlation between them.²⁴ Similar trends are seen also in England and Wales, where national health policy has discouraged PSA screening, and where the use of radical treatment has been less common than in the U.S.²⁴ However, the decline in PC mortality has been greater in the U.S., reflecting the different magnitude of the trends.²⁵ Collin et al reported that age-specific and age-adjusted PC mortality peaked in the early 1990's at almost identical rates in both the U.S. and the UK, but age-adjusted mortality in the U.S. declined after 1994 by -4.17% each year, four-times the rate of decline in the UK after 1992 (-1.14%). The greater decline in PC mortality in the U.S. compared with the UK in 1994-2004 coincided with a much higher uptake of PSA screening in the U.S.²⁵

Mortality trends have been estimated in the five Nordic countries. Mean annual declines in PC mortality of 1.8-1.9% were observed from 1996-2004 in Finland and Norway. During the same period, mortality rates leveled off in Iceland and Sweden but continued to increase in Denmark. In all the Nordic countries, except Denmark, has PSA testing and curative treatment been more frequently practiced since the late 1980's.²⁶

Consequently, many authors have interpreted the international trend patterns as indirect evidence for the efficacy of PSA-screening. Furthermore, after the introduction of PSA, the average age at diagnosis has fallen, the proportion of advanced stage tumors has declined and patterns of care have changed accordingly.¹⁹

Why has prostate cancer mortality declined?

Several explanations for the decline in PC mortality have been proposed. PSA screening was suggested to have led to a harvesting of prevalent cases of patients with subclinical PC, thereby increasing the population of men whose death could potentially be attributed to this disease.⁸ Once the pool of prevalent latent cancers was reduced, the number of men who could have PC assigned as cause of death was also reduced. Even before the PSA era, there was an increased interest in early detection with DRE. This, together with increased radical prostatectomy rates as well as the availability of other improved treatment options might have contributed to the changes seen.¹⁹ Increases in PSA screening and better treatment of early-stage disease, possibly acting in combination, remain plausible hypotheses.²¹ The frequency of aggressive curative treatment for early-stage disease with surgery as primary treatment has increased and radiation therapies have evolved enormously since the late 1980's.²⁷⁻³¹ The pattern of

androgen-deprivation therapy usage has changed.³² Treatments previously reserved for metastasized disease are now being used as adjuvant or neo-adjuvant therapies for localized disease.^{8, 25-26} The increased use of hormonal therapy is, most probably, also contributing to the observed changes in mortality.³² Hormonal therapy can postpone PC death long enough for the patient to die from unrelated causes³³.

Some authors have claimed that the observed decrease in prostate-specific mortality within the first decade after the onset of PSA testing came too early, given the long natural history of the disease.¹⁹ The observations of improved PC survival have been suggested as having been caused by so-called “lead-time bias” (referring to the phenomenon that screening may appear to improve survival, when it only advances diagnosis).³⁴ In a simulation model, Etzioni et al indicated that only short lead times (≤ 3 years) could produce a decline in PC mortality, through PSA testing, of the magnitude that was observed in the U.S.³⁵ Surveillance models suggest that PSA screening explains a significant fraction, but not all, of the drop in PC mortality seen.³⁶

One could also discuss lifestyle or health behavior, exposure and environmental changes. Other possible explanations include changes in co-morbidities and competing causes of deaths as well as changes in the risk of death from PC²⁴. Obesity, for instance, has been associated with an increased risk of PC death.³⁷ It has further been observed that the mortality from several malignancies, in general, has fallen.²⁹

The fact that the decline in PC mortality was preceded by an initial increase in both the incidence and mortality of PC could have introduced an artifact of its own. There might thus have been a bias related to the misattribution of cause of death, so-called attribution / classification bias. The likelihood of classifying PC as underlying cause of death for a non-PC death, could have been increased in PC patients because of the increased detection of PC.^{25,38} Such phenomena could have been reflected in the trends.

To sum up, PSA screening has clearly affected PC incidence and mortality patterns around the world. However, these trends are complex products of several changes over time, including changes in diagnosis and treatment, and it is extremely challenging to determine the causal relationships. Whether PSA screening reduces mortality is difficult to establish in epidemiological (observational) studies, and it is being investigated and reported in randomized controlled screening trials (see below)³⁹⁻⁴⁰.

1.3. The Prostate-Specific Antigen test, PSA

The test used in screening for PC is called Prostate-Specific Antigen (PSA) and was first isolated and defined in the 1970's⁴¹⁻⁴³. It is an androgen-regulated glycoprotein, a serine protease⁴⁴ and a member of the tissue kallikrein family⁴⁵. It is produced mainly by the prostate epithelium (with the majority of glandular tissue located in the peripheral zones of the prostate) and transported with seminal fluid. PSA is inactivated by forming complexes with protease inhibitors (“complexed” or “bound” PSA), mainly alfa-1-antichymotrypsin⁴⁶ and to a lesser extent alfa-2-macroglobulin and alfa-1-antritrypsin. 10-30% remains uncomplexed, but is inactivated by internal proteolytic cleavage (“free”

PSA). The biologic function is in regulating the degree of liquidity of the seminal coagulum by cleavage of semenogelins, hereby influencing the motility of the sperm⁴⁷.

In humans, the normal prostate glandular architecture consists of a single layer of secretory epithelial cells, surrounded by a basal layer and a basal membrane that separates the intra ductal PSA from the capillary and lymphatic drainage of the prostate. Normally, PSA leaks into the peripheral blood circulation in small proportions; the amount in serum is approximately one million fold lower than in prostatic fluid. Serum PSA normally increases with age⁴⁸. PSA may be found in an increased amount in the peripheral blood of men who have prostatic disease or mechanical manipulation interfering with the natural barrier between the prostate and the capillaries.

PSA as a marker for prostatic disease

A characteristic early feature of PC is disruption of the basal cell layer and basal membrane, i.e. the normal architecture, allowing a greater fraction of the PSA produced to have access to the systemic circulation. This, together with a decrease in the luminal cleavage processing causes relative increases serum PSA.⁴⁷ An increased cell turn-over or other mechanisms may play a role. Consequently, PSA is a marker for PC.⁴⁹ However, PSA levels in serum may also be high in men who have a benign prostatic hyperplasia (BPH, an enlarged, but noncancerous prostate)⁵⁰ or acute inflammation of the prostate (prostatitis). There is thus an overlap in total PSA levels between healthy men, BPH patients and PC patients. This may be due to the fact that the level of PSA expression on a per-cell basis is lower in PC cells than in normal prostate epithelium⁵¹⁻⁵². High PSA levels in men with advanced PC reflects the large number of tumor cells. A number of other factors can affect the PSA level, known to any urologist, such as urinary tract infections, indwelling catheters, rigid cystoscopy or 5-alfa-reductase-inhibitors.

Historically, the utility of the PSA as an adjunctive tool in the diagnostic arsenal for PC was first proposed in 1980, when Kuriyama et al. found that men with PC (and BPH) had elevated PSA levels compared to both healthy men and healthy women and compared to both men and women with other (non prostatic) malignancies⁵³. The PSA therefore came to replace the earlier prostatic acid phosphatase (PAP) because it was found by Stamey et al. to be more sensitive than PAP in the detection of PC⁴⁹.

PSA is neither specific to the prostate, nor cancer-specific. Although it is almost exclusively produced by the prostate epithelium, some tissues can also contain PSA. It has been found in breast tissue/tumors⁵⁴⁻⁵⁵, colon, liver, kidney, adrenal and parotid tumors⁵⁶, in ovarian teratomas⁵⁷, in skin tumors⁵⁸ and in male salivary gland tumors⁵⁹. It can also be found in male periurethral and male perianal glands⁶⁰⁻⁶², however, these do not seem to have a clinically significant effect on serum PSA⁶³. As there is no significant source of serum PSA outside of the prostate gland, serum PSA can be used to monitor the clinical course of PC, to monitor the efficacy of definitive local therapy, as an early indication of PC recurrence and to monitor response of hormonal therapy (androgen-deprivation).⁴⁷ Undoubtedly, no tumor marker has caused such a significant change in the approach to cancer detection, staging and monitoring following therapy as PSA⁸.

Specificity, sensitivity and positive predictive value

“Background noise” from BPH-related PSA elevation implies that the specificity of the PSA as a screening test for PC is not ideal.⁶⁴ The PSA has been questioned as a screening tool for PC for possessing a low likelihood ratio (imperfect to “rule in disease”).⁶⁵ The sensitivity and specificity of the test depend on laboratory assay and method, PSA range in population studied, biopsy criteria and percentage biopsied. The specificity of the test, with a PSA cut-off of 3 ng/mL, is reported to be as high as 89%, (i.e. the proportion of the healthy population who have a negative test).⁶⁶ The positive predictive value in the Göteborg screening study is reported to be approximately 24% (i.e. the proportion of men with a “positive” test result who actually have the disease), thus 76% are “false-positives”.⁶⁶ The positive predictive value of a biopsy (measured as the number of cancers detected on screening divided by the number of biopsies expressed as a percentage) was on average 24% (range 18.6 – 29.6) in the European Randomized Study of Screening for Prostate Cancer, ERSPC (see below).³⁹ This means that many men will undergo prostate biopsies to rule out cancer. The proportion of positive screening tests (mainly PSA > 3 ng/ml, but a cut-off of 4 ng/ml and DRE/transrectal ultrasound findings and free to total ratios were used in some centers) was 16.2% (with a range of 11.1 to 22.3% among the centers). The average rate of compliance with biopsy recommendations was 85.8%.⁶⁶

A single PSA test as a screening tool

To eliminate the effect of BPH-related PSA elevations and to find ways of improving PC detection, Lilja et al. conducted a case-control study in men aged ≤ 50 years, a group of men in which BPH was not yet high-prevalent. Between 1974 and 1986, 21,277 men enrolled in a cardiovascular study provided blood samples. They constituted a screening naïve population in Malmö, Sweden, as Swedish national guidelines have long advised against PSA screening.⁶⁷ PCs were identified up to 25 years later from the Swedish cancer registry and most cases were clinical tumors (76% T2, T3 or T4). Men with PSA levels between 2-3 ng/mL had a 19-fold increase in odds for PC compared to controls. Of advanced detected tumors (T3, T4 or metastasized at diagnosis), 80% occurred among men with a PSA above the median already at age 44-50 years.⁶⁸

Other diagnostic tools or combinations of markers

Other diagnostic tools to improve specificity have been proposed. Presumably because of disruption of the normal secretion of PSA into the excretory ducts in PC tissue, the proteolytic cleavages that occur in seminal fluid that make PSA inactive (“free”) are present at lower levels in PC tissue. Consequently, the ratio of free to total PSA (fPSA/tPSA, termed the PSA ratio) is lower in many patients with PC and seems to aid in the discrimination between BPH and PC, thus increasing the specificity of the test in men with slightly elevated PSA (3-4-10ng/mL)^{69, 70-72}. Other ways to increase specificity have been suggested, such as PSA density (PSA/prostate gland volume)⁷³ as higher PSA levels are seen in men with larger prostates⁷⁴ and age-specific PSA cut-offs as PSA

increases with age⁴⁸. The former has been criticized because the value is dependent on who performs the TRUS and the latter because there is a risk of excessive biopsy in younger men and under-diagnosis of advanced cancer in older men. The majority of PCs detected because of an elevated PSA are too small to be seen as hypo-echogenic lesions on TRUS. The value of ultrasound in itself is in measuring prostate volume and in improving the accuracy in the systematic sampling of biopsies.

Multiple kallikreins (total, free, intact PSA, and human kallikrein-related peptidase2) measured in blood has been shown to predict the result of biopsy in previously unscreened⁷⁵ and screened⁷⁶ men with elevated PSA and to reduce the number of men who have to undergo biopsies without missing many significant cancers.

The Prostate Health Index (*phi*) combines total PSA, free PSA and [-2]proPSA into one index that estimates a man's probability of having PC found on biopsy. Phi may add significant information regarding individual patient risk and may be used as an aid in patient management⁷⁷. PCA3 (Prostate Cancer gene 3) is a gene which messenger RNA (mRNA) is over-expressed in the majority of PCs⁷⁸. An assay has been developed that detects this mRNA in urine to help make better biopsy decisions⁷⁹.

What is a 'normal' PSA?

The optimal cut-off value in PSA screening has been discussed. A higher PSA threshold would minimize the number of negative biopsies (optimize specificity), but perhaps miss cancers ('under diagnosis'), whereas a lower PSA threshold would maximize the number of cancers detected (optimize sensitivity) but perhaps diagnose too many indolent cancers ('over-diagnosis'). For over two decades, a PSA-cut-off of 4 ng/mL was used as a screening tool in early detection of PC. The Prostate Cancer Prevention Trial (PCPT) in the U.S. changed this. In 2004, Thompson et al. reported outcomes for 2,950 men with a PSA less than 4.0 ng/mL and who had an end-of-study biopsy after 7 years. Of these, PC was found in 15.2%. Of these, 15% had a Gleason score^{1*} of 7 or higher (i.e. high grade disease). Of all tumors, 27% were detected in the PSA range between 3.1 and 4.0 ng/mL, and every fourth tumor among these was high grade disease.⁸⁰ Therefore, Thompson et al. could conclude that there was no lower limit of PSA at which PC could not be detected and that the PSA level should reflect a level of risk of PC and not be regarded as a dichotomous marker ('positive' or 'negative'). This finding was a stunning revelation to the urologic and medical community; no longer was the PSA "normal" or "elevated".⁸ Lodding et al. showed that lowering the PSA cut-off from 4 to 3 ng/mL in the Göteborg prostate screening trial increased PC detection by 30%, with most of these cancers clinically significant.⁸¹

^{1*} Gleason score (GS) (after Donald F Gleason 1920-2008) is the pathological grading of prostate needle biopsies, TURP and radical prostatectomy specimen. It is based on the sum of the two most common morphological Gleason grades(GG)/patterns under the microscope, but after the 2005 ISUP Consensus Conference on Gleason Grading a modified GS has been suggested so that needle biopsies includes tertiary patterns (i.e. GS = the dominant + worst pattern).

1.4. Screening

Several definitions of screening have been proposed. The World Health Organization (WHO)⁸² states:

*“The use of simple tests across a healthy population
in order to identify individuals who have a disease
but do not yet have symptoms.”*

The PSA is a simple, and inexpensive test and biomarker of PC⁴⁹ that is used as a screening tool in detecting early PC among asymptomatic men⁸³. The aim of general screening should be to diagnose and treat PC as early as possible, but at the same time, as “late” as possible to prevent a man from long-time suffering from the negative side-effects of treatment. Hence the test should diagnose the disease with the aim of identifying men who would benefit from it, without being brought to harm. The diagnosis should, ideally, lead to reduced morbidity as well as reduced PC mortality.

Diagnostic procedures

To obtain the diagnosis of PC, the main tools in the diagnostic arsenal include digital rectal exam (DRE), PSA and transrectal ultrasonography (TRUS). Most PCs are located in the peripheral zone of the prostate and detectable by DRE when the volume is larger than 0.2 mL. A suspect DRE alone can detect PC in about 18%⁸⁴. A hypoechoic area on TRUS may be indicative of PC and biopsies targeted at this area may be useful. The only means of verifying the definite diagnosis is the presence of adenocarcinoma in prostate biopsies, or from specimens from transurethral resection, or radical prostatectomy. A transrectal approach is used for most prostate biopsies, but some urologists use a perineal approach. Sextant biopsies have long been the gold standard for sampling; however, 10-core biopsies are recommended today⁸⁵. Saturation biopsies (average 24 cores) detect PC in about 40%⁸⁶. Ultrasound-guided peri-prostatic local anaesthesia and antibiotic prophylaxis with quinolones are state-of-the-art. TRUS-guided transrectal core biopsies are favored over fine-needle aspiration biopsy because fewer pathologists are trained in cytology. Core biopsies also provide information on the histopathological grading (see Gleason score below) and the extent of the tumor. Complication rates after biopsy are low. Minor complications include macrohaematuria (15% > 1 day) and haematospermia (37%). Severe infections (fever, urosepsis) have been reported in < 1% of cases. Rectal bleeding occurs in about 2%.⁸⁵

History of prostate cancer screening

The initial reports of PSA screening as compared to digital rectal exam (DRE) alone, those of Catalona et al., Wang et al., Cooner et al., Brawer et al. and Stamey et al.^{49, 83, 87-89}, in populations that had never been examined with a screening test before, set the stage for a widespread adoption of the test that led to an increased rate of PC detection as was seen across the U.S. between the late 1980's to the early-mid 1990's.⁸ Many medical

organizations agree today that appropriate candidates for screening include men older than 50 years of age and men over 40 years at increased risk (for example family history or race) for PC, but that screening is unlikely to benefit men who have a life expectancy of less than 10 years. These organizations include the American Academy of Family Physicians, the American Cancer Society, the American College of Physicians, the American Medical Association, and the American Urological Association.⁹⁰ The latter recommend the age for obtaining a baseline PSA to be 40 years for all men.⁹¹ These organizations recommend that clinicians discuss with patients the potential benefits and possible harms of PSA screening, consider patient preferences, and individualize the decision to screen.

Today's national recommendations

However, the U.S. National Cancer Institute (NCI) does not recommend general PSA screening and the U.S. preventive services task force (USPSTF) has concluded that the current evidence is insufficient to assess the balance of benefits and harms of PC screening in men younger than 75 years, and they recommend against screening for PC in men of 75 years or older.⁹² In Sweden, screening for PC is recommended to men who have two or more first-degree relatives with the disease. These men have an increased risk of a PC diagnosis before the age of 70⁹³⁻⁹⁴. In these men, screening (information, PSA, DRE) is recommended to start at 40-50 years.

In 1995, the Swedish Council on Technology Assessment in Health Care, internationally known by its Swedish acronym "SBU" (Statens Beredning för medicinsk Utvärdering) published a report on general screening for PC ("*Massundersökning för prostatacancer*")⁹⁵. It was concluded that screening for this disease could not be recommended, mainly due to the absence of convincing evidence from randomized trials on the benefits of early detection. More evidence has been published since the first SBU-report, but no change in current practice is predicted within the immediate future. The issue is discussed continuously in The National Board of Health and Welfare.

1.5. Randomized controlled screening trials

In a Cochrane review from 2007⁹⁶ on screening for PC, Ilic et al. identified 99 potentially relevant articles, of which two randomized controlled trials (RCT) met the inclusion criteria (i.e. screening versus no screening or routine care for PC); the *Quebec trial* that was commenced in 1988 by Labrie et al. (PSA and DRE, PSA > 3 ng/mL as cut-off, men aged 45 to 80 years, 2:1 randomization)⁹⁷⁻⁹⁸ and the *Norrköping trial* that was commenced in 1987 by Sandblom et al. (screening with DRE every three years in the first two screening rounds, 1987 and 1990, and DRE and PSA in 1993 and 1996, with DRE-findings or a PSA > 4 ng/mL as biopsy triggers, men aged 50 to 69 years)^{99,100}. Both trials had limitations in their study methodology.

The Quebec trial

In the Quebec trial, firstly, only 23.6% were screened in the group invited (7,348 of 31,133 men), and such a low adherence rate reduces the power of the study to detect a true difference that could be attributable to screening. In the control group, 7% were estimated as having been screened. Secondly, the data analysis presented was not performed according to the intention-to-screen principle. Instead, mortality from PC was analyzed for the number of men who actually underwent screening as compared to those that did not undergo screening, regardless of their initial group allocation.⁹⁶

The Norrköping trial

The Norrköping study was smaller, encompassing 1,494 men randomized to screening and 9,026 controls (with every sixth man assigned to the screening group from a list of birth dates obtained from the national population register, described by Ilic et al. as 'quasi-randomized'). Further, information regarding the study was distributed through newspaper, radio and television broadcasting. This could have raised a potential for self-selection bias and contamination in the control group, with control participants also seeking screening.⁹⁶ Furthermore, the Norrköping study was originally designed as a feasibility study to study the acceptability, organization and consequences of a screening program.⁹⁹ Therefore, Ilic et al. concluded in the review that in order to make evidence-based decisions, more studies were needed on firstly, the effect on PC mortality, and secondly, the impact on quality of life, economy and the harms of screening.

The Stockholm trial

Yet another screening study has been conducted in Stockholm, Sweden. Commencing in 1988, a total of 2,400 men of 55-70 years were randomly selected and invited to a one-time screening for PC. Of these, 1,782 (74%) attended. Participants were examined with DRE, TRUS and PSA. If they had abnormal findings on DRE and/or TRUS, they underwent randomized quadrant biopsies as did men with a PSA > 10 ng/mL. If the PSA was greater than 7 ng/mL, repeat TRUS was performed. Men with PC were offered the standard care of that time. With this protocol, a single intervention done in a previously screening naïve population revealed many PCs advanced at diagnosis ('prevalent screen'). At a median of 12.9 years of follow-up, there was no effect seen on the risk of death from PC and other causes of death when all the men invited were compared with the source population of 27,204 men (incidence-rate ratios 1.10, 95% CI 0.83–1.46 and 0.98, 95% CI 0.92–1.05, respectively).¹⁰¹

1.5.1. The ERSPC trial, The Göteborg trial and the PLCO trial

To further evaluate the effectiveness of PC screening, two large-scale randomized population-based trials including men aged 55 – 74 years were initiated in the early 90's: the *European Randomized Study of Screening for Prostate Cancer (ERSPC)*, <http://www.controlled-trials.com> number ISRCTN49127736) in Europe and the *Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO)*, <http://www.clinicaltrials.gov> number, NCT00002540) of the National Cancer Institute (NCI) in the U.S.¹⁰² Hereafter, the acronym "PLCO" will refer in this thesis to the prostate section of the study only.

The studies are still ongoing. A few interim analyses have been made throughout the years and main end-point result reports have been published (see below). In the United Kingdom, another ongoing trial, the Comparison Arm for the Prostate Testing for Cancer and Treatment study, combines the assessment of screening and treatment.

Background ERSPC

After a series of pilot studies from 1991 to 1993, the final screening study of ERSPC was initiated in 1994 and includes eight European countries. The countries are: the Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland and France. The ERSPC is the world's largest ever randomized study of screening for PC, in which nearly 73,000 men were randomized to screening and nearly 90,000 men were randomized to serve as controls, aged 50–74 years. In the first main outcome report (PC mortality) in 2009, results were reported for 162,387 men in the core age group of 55-69 years in 7 of the 8 countries (excluding France)³⁹. The participating countries and the size of the study sections of the ERSPC in this publication is illustrated in figure 3.

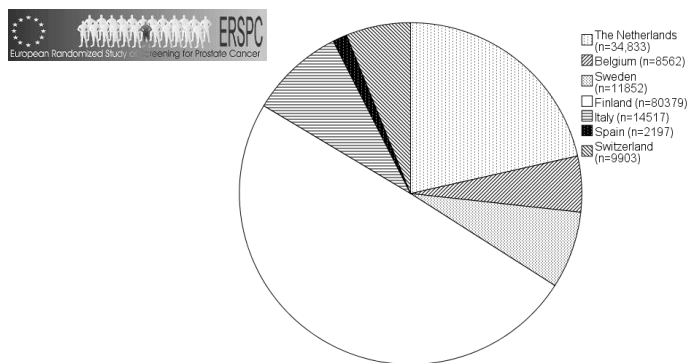


Figure 3. Proportion of subjects per study center in the core age groups of the ERSPC trial in the 2009 *New England Journal of Medicine* publication (in which France was not included). Adapted from [Schröder FH et al. *NEJM*. 2009;360:1320-1328] <http://www.erspc-media.org/>

The screening interval is 4 years, with the exception of Sweden where screening is biennial (every 2 years). Screening is PSA driven: a biopsy is indicated for men who have a PSA level of 3.0 ng/mL or higher (initially, in some centers, suspicious DRE or TRUS or a low ratio of F/T PSA < 16% in men with PSA 3.0 – 3.99 ng/ml were also indicators for biopsy). The Netherlands and the Göteborg sections of the ERSPC are, this far, the most extensively studied. The study and the related quality of life-research should result in evidence-based advice to governments around the world¹⁰³.

Background The Göteborg trial

The Göteborg Randomized Prostate Cancer Screening Trial was approved by the ethical review committee of Göteborg University in 1994. Professor Jonas Hugosson at the department of urology at Sahlgrenska University Hospital is the principal investigator. As of Dec 31, 1994, the population register documented 32,298 men born between 1930 and 1944 (age 50–64, median 56 years) living in the city of Göteborg, Sweden. By computer randomization 20,000 of these men were identified and allocated (1:1 ratio) to either the intervention arm (screening group) or to a control group. The study was planned independently from the ERSPC during 1993-94. After approval from the Ethical committee in 1994, the study started to invite men in January 1995. The power of the study was calculated upfront and it was not planned as a sub-study within the ERSPC. During the autumn 1995, the study board of the Göteborg trial was invited by the Principal Investigator of the ERSPC, Professor Fritz Schröder (the Netherlands), to the ERSPC meetings. The ERSPC accepted the Göteborg protocol without any changes and in 1996 the Göteborg (=Sweden) section agreed to join the ERSPC study with men in the core age group, which includes 11,852 men (59%) of all men randomized in the Göteborg trial. In the first main endpoint report from the ERSPC in 2009 the Göteborg section represents 11,852 of the 162,243 men (7.3%)³⁹.

Background PLCO

The prostate component of the PLCO trial (figure 4) was initiated in the U.S. in the early 90's. The study randomly assigned 76,693 men (aged 55 – 74) to either screening or controls (usual care). Men who were assigned to the screening group were offered annual PSA testing for 6 years and annual digital rectal examination for 4 years. Men with a PSA value >4 ng/mL or suspicious findings on the DRE were advised to seek diagnostic evaluation, which in accordance with standard practice in the U.S. was at the discretion of the patient and his primary physician.⁴⁰



<http://prevention.cancer.gov/plco>

Figure 4. The Prostate, Lung, Colorectal & Ovarian cancer screening trial

1.5.2. RCT's – Results

The major results of the world's two largest randomized PC screening trials were awaited for several years. The first reports on the major end-points from these two trials were published in the same issue of the *New England Journal of Medicine* in early 2009. However, as Holmberg wrote in an editorial: "No one professionally involved in PC diagnosis and treatment would have expected the first analyses of the ERSPC and the PLCO to provide the final answers to all major questions in PC screening."¹⁰⁴ A thorough report of the differences between these two trials is presented by Schröder and Roobol in 2010.¹⁰⁵

ERSPC

Earlier comparisons of the characteristics of PC detected in both arms of the ERSPC have given an indication of the immediate effects of screening on down-staging of the disease. An analysis in 2005 yielded the result that in the screening arm of the Netherlands' section of the ERSPC the following characteristics were seen (as compared to the control arm): lower PSA at diagnosis, a favorable shift in Gleason score, lower stage, and a decrease in the diagnosis of metastatic disease¹⁰⁶. Hence there was already confirmatory evidence that screening results in the identification of cancers with favorable characteristics.¹⁰⁷ That PSA screening reduces the risk of being diagnosed with metastatic PC, the first prerequisite for achieving decreased PC mortality in younger men, has also been shown in the Göteborg trial.¹⁰⁸

These early findings of a favorable effect of PSA screening were confirmed when the first results on PC mortality from the ERSPC were published in 2009.³⁹ Encompassing 7 out of 8 countries in this analysis and 162,000 men in the core age group of men aged 55 to 69 years, it showed that PSA driven, continuous, PC screening reduced PC mortality by 20% after a mean follow-up of 8.8 years (214 men out of 72,890, 0.29%, in the screening group died of PC compared to 326 men out of 89,353, 0.36%, in the control group, or RR 0.81, 95% CI 0.65 to 0.98, $p=0.04$ adjusted for alpha-spending). Adjustment for non-compliance resulted in an even greater effect of 27% among those screened³⁹, and additional adjustment for contamination led to an estimated reduction of up to 31%.¹⁰⁹ There was a reduction in the incidence of advanced PC stage at diagnosis in the screening group. The proportions of men who had a Gleason score of 7 or more were 27.8% in the screening group and 45.2% in the control group. Men in the screening arm were almost three times more likely than men in the control arm to undergo radical prostatectomy and twice as likely to receive radiation therapy¹¹⁰. From the results of the ERSPC, it could be calculated that 1,410 men (or 1,068 men who actually underwent screening) are needed to be screened to have 48 PCs treated or managed, to prevent one man from dying from PC.

PLCO

The PLCO could not corroborate the finding of the ERSPC. After 7 to 10 years of follow-up, the rate of death from PC did not differ significantly between the two study groups. At 7 years, the rate ratio of PC mortality in the screening group as compared to the control group was 1.13 (95% CI, 0.75 to 1.70) and through year 10, with follow-up complete for 67% of the subjects, the rate ratio was 1.11 (95% CI, 0.83 to 1.50).⁴⁰ There may be several explanations for this outcome:

1. Sample size

Firstly, the PLCO was smaller. Its sample size was only 77,000 individuals in total, which critically compromised the power of the study to detect any difference between the groups as regards PC mortality (see below, point 3).

2. Dilution and contamination – screening in the control group

Secondly, both the screened group and the control group in the PLCO consisted of around 30% of men who were already pre-screened ('dilution') with both DRE and PSA within the past three years before study start. Furthermore, the proportion of PSA-screened men in the control arm was as much as 52% by the sixth year ('contamination').⁴⁰ This could be compared with the compliance in the screening group, in which 85% had a PSA test. It could be questioned whether the narrow 33% difference in testing was sufficient to show an effect on PC mortality.

3. Power calculation

The power of the prostate section of the PLCO trial was calculated to amount to 91% and 98% to show a 25% and 30% PC mortality reduction respectively, by recruiting 37,000 men to each trial arm. This was, however, under the assumption of a 100% compliance rate and one-sided hypothesis testing ($p \leq 0.05$ considered statistically significant). From the original study protocol of the PLCO¹⁰², at least a 90% compliance and only a 20% contamination would have yielded a disease-specific mortality reduction of 27%. The reality instead was completely different. Screening was compared to men "following their usual medical care practice"¹⁰⁵. The study could therefore, even initially, be regarded as underpowered, as a study of that sample size and of the ages of 60-74 years, with a compliance maximum of 50% and a contamination of at least 40% would have required – from the initial power calculations – an unrealistic disease-specific mortality reduction of 90%. However, one can wonder why the substantial difference between the study investigators' initial claims and the actual performed reality in the PLCO study was not communicated in the medical literature and to the media? (Recker F. personal communication)¹¹¹ In the main endpoint publication of the PLCO⁴⁰, no reference to the initial power calculation was given in the discussion.

4. Prostate cancer incidence

As a result of the widespread PSA testing in the control group, there was only a modest increase in the excess numbers of PC detected in the screening group, compared to what one might have expected. At 7 years, screening was associated with a relative increase of 22% in the rate of PC diagnosis, as compared with the control group (RR 1.22, or 2,820 PCs in the screening group, as compared to 2,322 in the control group). In the ERSPC, there were instead about twice (1.71) as many cases of PC diagnosed in the screening group as in the control group in the ERSPC trial (5,990 PCs in the screening group or a cumulative incidence of 8.2% as compared to 4,307 PCs in the control group, or a cumulative incidence of 4.8%) indicating the lesser contamination in the ERSPC study (at least during the early years of the study, estimated at 3-6% to the range of 15%¹⁰⁵) than in the PLCO study. When the ERSPC was initiated, in Europe, the perceptions of the value of early detection were different compared to those of the U.S.

5. Follow-up of positive screening tests

Contributing to the difference in incidence could have been the fact that in the PLCO, there was no systematic follow-up with clinical examination including TRUS and prostate biopsies for screen-positive subjects, as in the ERSPC. Instead, men with positive results of the PSA test or suspicious findings on the DRE were advised to seek diagnostic evaluation. In accordance with standard U.S. practice, diagnostic evaluation was instead decided by the patients and their primary physicians. In the ERSPC, the average rate of compliance with biopsy recommendations was 85.8%, as compared to the PLCO, in which only 40% of men had a biopsy.

6. Low prostate cancer mortality rates

The fact that approximately 44% of the men in each study group had undergone one or more PSA tests at baseline, could have eliminated some cancers detectable on screening from the randomized population, especially in health-conscious men (who tend to be screened more often). The authors reported that the cumulative death rate from PC after 10 years in the two groups combined was 25% lower in those who had undergone two or more PSA tests at baseline than in those who had not been tested.⁴⁰

At 7 to 10 years of follow-up in the PLCO, the rate of death from PC was low and did not differ significantly between the two study groups. Although the numbers were small, there were actually even more PC deaths in the screening group (50 or 0.13% of all screened men vs. 44 of 0.12% of all controls in year 7 and 92 out of 38,343 vs. 82 out of 38,350 in year 10), however, this was non-significant (and the confidence intervals around the estimates were wide). The numbers of outcomes were somewhat modest. This limitation makes a statement about PC mortality difficult. At 7 years of follow-up, the rate ratio of death attributed to PC was 1.13 (95% CI 0.75 to 1.70) and at 10 years the corresponding figure was 1.11 (95% CI 0.83 to 1.50).

7. Follow-up time

Although the median duration of follow-up was 11.5 years (range, 7.2 to 14.8) in the PLCO, this is a comparatively short period for a disease such as PC, given its natural history. Follow-up was complete, i.e. vital status was known for 98% only at 7 years. After this period, the ERSPC did not reveal any mortality difference either. At 10 years, only 67% of subjects had a complete follow-up.

8. Stage distribution

Interestingly, despite more PCs being found in the screening group as compared to the control group (at 10 years 3452 versus 2974 PCs, rate ratio, 1.17), there was no difference in the stage distribution between the two trial arms of the PLCO⁴⁰. A difference in the incidence of metastasized disease is a prerequisite for finding a mortality difference in younger men¹⁰⁸.

9. PSA cut-off

Another possible explanation for the lack of PC mortality reduction in the PLCO study could have been the PSA cut-off level of 4 ng/ml as a biopsy indication, as compared to 3 ng/mL in the ERSPC, where this reduction was seen. By using a higher criterion, one may miss some potential PCs and potentially some lethal ones. The screening algorithm was also different, in that in the PLCO, subjects who were assigned to the screening group were offered annual PSA testing for 6 years and annual digital rectal examination for 4 years.¹¹²

10. Lead time

Furthermore, by estimations from graphical comparisons of the cumulative PC incidence curves between the two arms, the lead time in PLCO was calculated to an average of only 2 years, as compared to 4.5 years in the ERSPC. Such a short lead time as 2 years in the PLCO suggests a strong similarity between the screening arm and the control arm. Alternatively, a lead time of 4.5 years in the ERSPC shows the superior quality of the latter study.¹¹³

11. Improvements in therapy

Moreover, during the course of the PLCO trial, there were also improvements in early therapy for PC¹¹⁴, that could have resulted in fewer PC deaths in both study arms and hence may have blunted any potential benefits from screening.⁴⁰ Aggressive radical treatment in both arms that concomitantly improved prognosis would make further improvements with a screening trial difficult.¹⁰⁴

12. Follow-up of abnormal screening tests

Furthermore, yet another proposed reason why the PLCO failed to demonstrate a mortality benefit may have been the considerable delays in the follow-up of abnormal screening test results (median days between screening and first biopsy). In the PLCO,

the follow-up of abnormal screening results (when, how, by whom and which treatment) was at the discretion of the men's physicians (the PLCO trial did not specify a diagnostic algorithm), and most men with abnormal screens were either not recommended, or chose not to undergo, immediate biopsy. The frequency of delayed biopsies resulted in that many cancers were diagnosed more than a year after an initial positive screening test.¹¹² Men who died from PC also had a significantly greater delay in undergoing biopsy following abnormal test results, suggesting that this may be an important factor behind the negative findings of the PLCO trial.¹¹⁵ In a case-case analysis of men who died from PC compared to those who did not, disease-specific death was associated with a lower frequency of DRE and PSA testing.¹¹⁵

In the ERSPC trial, the execution of prostate biopsies was performed within the screening centers, strictly following the defined biopsy indications. The difference in compliance with biopsy indications between the ERSPC and the PLCO resulted in dissimilar stage and grade distributions of the tumors detected.¹⁰⁵

1.5.3. RCT's – Implications and over-diagnosis

The first reports on PC mortality from the ERSPC and the PLCO were conflicting. Any final conclusion was difficult to draw, despite one first 'level 1 evidence' that PC screening reduces PC mortality. Fears still remain that the negative aspects of screening are substantial. While several publications on the potential benefits of screening are now reported, the degree of harm remains to be established.

Some studies have indicated that most PCs detected via PSA are believed to be clinically important, based on the findings that the pathological features do *not* resemble those of autopsy cancers¹¹⁶⁻¹¹⁷. With the results from the ERSPC, we know that there is a window of opportunity where early treatment can affect the natural history of PC. However, this is not true for all PCs detected. Fears persist that a considerable percentage of screen-detected PCs are indolent and do not need to be detected at all (or can still be detected later at a curable stage).¹¹⁸

Over-diagnosis

One potential problem connected with early detection is the risk of so-called *over-diagnosis*. By this we refer to cancers that are otherwise not diagnosed during a lifetime¹¹⁹⁻¹²⁰, it can alternatively be defined as cancers that will not lead to death¹²¹.

Although the Gleason score (histopathological grading of PC) is a good prognostic factor of PC-survival¹²²⁻¹²³, and a strong predictor of the natural history, to date, there are no prognostic parameters in biomaterials (urine, blood or prostatic tissue) that can predict the *exact* outcome of every PC. Prognostic models have been established by adding several features together. According to a prognostic nomogram, a man with the features of an organ-confined, less than 0.5 cubic centimeter and well-differentiated PC has a high chance of having an indolent tumor.¹²⁴

In computerized simulation models, over-detection rates in PSA screening have been estimated to vary, depending on age span and screening algorithm, from around 15-40% (defined as the proportion detected through PSA screening, but who did not survive long enough to have their cancer clinically diagnosed, predicted by the simulation model, i.e. who were not estimated as dying of other causes during lead time)¹²⁵ to up to 50% (defined as the detection of irrelevant cancers, as the relative increase caused by screening, of the number of men with PC diagnosed during their lifetime).¹²⁰

However, when trying to understand the potential implications for a man of being over-diagnosed, PC mortality has been suggested as being a more important end-point than disease incidence or symptoms of disease, especially when the benefit of early treatment in many men with screen-detected PC has not yet been clearly established.¹²⁶ Earlier work by McGregor et al. used PC mortality from the screening literature as an end-point for calculating over-diagnosis and estimated that 84% of screen-detected PCs might be over diagnosed.¹²¹ The proportion of screen-detected PCs today that will be potentially lethal within < 20 years will be an issue for further prospective research.

Harms and benefits

Even if screening has been demonstrated to be effective in reducing PC mortality, the major challenges are to minimize this potential over-diagnosis and frequent concomitant risk of over treatment, together with attempts to differentiate between potentially progressive and non-progressive disease.¹²⁷

However, are the potential negative aspects from PC screening few enough and of such moderate magnitudes that screening can be justified – in the light of a reduced disease-specific mortality by 20% to up to 31% as now seen? Some authors have claimed that “even a modest 20% reduction in relative risk of suffering the atrocious consequences of metastatic disease and then dying from such a common cancer as PC is a worthwhile goal to consider”.¹⁰⁴

The debate surrounding PSA screening is still ongoing after the first reports. Studies with longer follow-up as well as more studies on the harms of screening are called for.

1.6. Risk factors for prostate cancer

Despite its being a common disease, the cause of PC is largely unknown. Several risk factors have been described¹²⁸, of which the best documented are age¹²⁹, ethnicity^{130,131} and heredity^{93-94, 132}. The incidence is 60% higher and the mortality rate is two-fold higher in black men compared to white men¹³⁰. A man whose father was afflicted by PC has a higher risk of being diagnosed with PC than a man without heredity⁹³. The risk is higher if a brother has the disease, and the younger the brother or the father was at diagnosis, the higher the risk⁹⁴. Men with hereditary forms of PC are at increased risk of PC death, mainly because they are more likely to acquire the diagnosis before 70 years.

Sexually transmitted infections (STI) have been variably, but in prospective studies only borderline associated with the risk of PC.¹²⁸ A retrovirus named XRMV, with a yet unclear route of transmission (blood or sexual transmission are plausible), has been linked to increased PC risk in genetically susceptible individuals.¹³³ If PC is shown to be an infectious disease, targets for prevention could include information, physical barriers, vaccines, antiviral agents/antibiotics or other strategies.

Geographic variability

There are striking variations in the risk of PC and the risk of dying from PC by geographic area (Figure 5). The majority of PC cases are seen in developed countries and these differences are likely to be due to the combination of variations in diagnostic uptake, detection and registration as well as genetics, different dietary habits and different exposures to carcinogens.

Similar geographic variations apply to the mortality risk (Figure 6). Among developed countries, the age-adjusted mortality rate for PC is among the highest in Sweden (21.4 per 100,000 men, in year 2008)¹³⁴, and among the lowest in Japan (5.0 per 100,000 men). The U.S. age-adjusted mortality rate falls in between (9.7 per 100,000).

These differences, together with migrant studies, suggest that environment, lifestyle and dietary factors may play important roles in the development of clinically detectable PC. Studies of Japanese migrants to the U.S. show that the incidence increases with time spent in the migrant country (to an intermediate level between the original and the host population).¹³⁵⁻¹³⁶ Some of this change reflects diagnostic differences, but a proportion is certainly due to changes in environment and/or diet. Observational studies suggest that differences in dietary habits explain 30% of the variation in the risk of different cancer forms in the Western world, and that the most prevalent cancers; prostate, breast and colon cancer co-vary to a large extent.¹³⁷

The international variations in incidence in men of similar ethnicity are compelling evidence that implies a potential for primary prevention. This, as compared to no prevention in a community, has been regarded as highly cost-effective by the National Board of Health and Welfare in Sweden⁹.

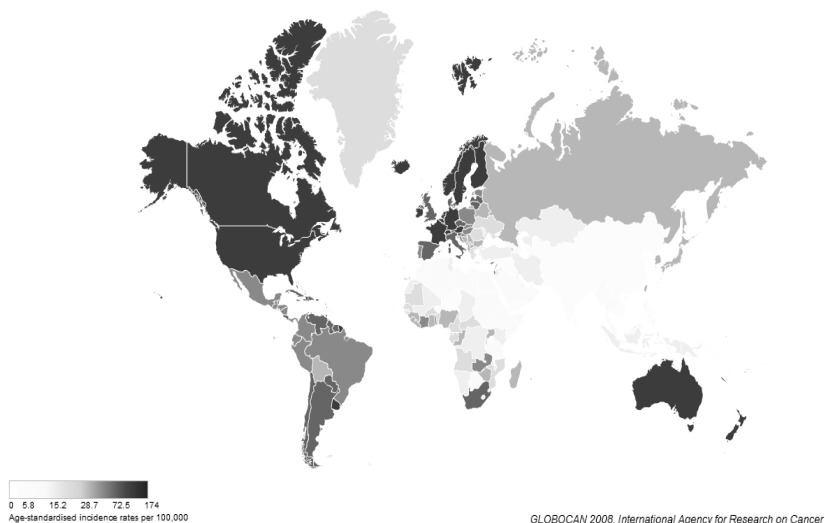


Figure 5. Prostate cancer incidence worldwide in 2008. Age-standardized incidence rates per 100,000. Dark colored areas have the highest incidence rates, with up to 173.7 per 100,000 whereas the areas with the brightest color have the lowest incidence, less than 8.8 per 100,000.

From Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available at: <http://globocan.iarc.fr>



Figure 6. Prostate cancer mortality worldwide in 2008. Age-standardized mortality rates per 100,000. Dark colored areas have the highest incidence rates, with up to 61.7 per 100,000 whereas the areas with the brightest color have the lowest incidence, less than 5.3 per 100,000.

From Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available at: <http://globocan.iarc.fr>

1.7. Primary prevention

“An ounce of prevention is worth a pound of cure.”
Henry de Bracton, *De Legibus* (1240)

This ancient and famous proverb was first recorded in Latin in 1240 and has been repeated ever since. PC is of great public health importance and its prevention would be a theoretically rational approach to diminish the patient-related, society- and health-related and economic impact of this disease. A couple of interesting primary prevention options have been suggested, however far they may be from being included in clinical practice today, 2010. A comprehensive review on the prevention of PC was published by Jayachandran et al. in 2008¹³⁸.

The androgen-prostate relationship

It has long been suggested that androgens and androgen metabolites play a role in PC tumorigenesis and the relationship between androgens and the androgen receptor has been studied extensively¹³⁹. Huggins was the first to study the androgen-prostate relationship. His pioneering work revolutionized the understanding of PC and heralded the era of drug therapy for PC, earning him the Nobel Prize in Physiology or Medicine in 1996¹⁴⁰. In the original study from 1941¹⁴¹, Huggins and Hodges (his student) showed that PC was receptive to androgenic activity and that metastatic PC was inhibited by eliminating circulating androgens; either by orchidectomy or by means of administration of estrogens (the latter, however, soon used less frequently because of an observed increase in thromboembolic and cardiovascular events). There are few scientific articles that have had such an impact. Various antiandrogens and later the GnRH (Gonadotropin Releasing Hormone) agonists and antagonists were developed after this early work. However, more recent findings show that the cellular mechanisms are complex and some studies have shown no association between circulating levels of androgens and PC risk¹⁴²⁻¹⁴³ suggesting a more intricate effect on a receptor level.

Chemo-preventives

One primary prevention strategy on the androgen theme is based on the fact that inhibitors of the enzyme 5- α -reductase, 5ARI's, that convert testosterone to the more potent androgen dihydrotestosterone, DHT, induce shrinkage of the prostate volume by approximately 30% in men with BPH. Studies of prostate biology support the concept that DHT is the principal androgen responsible for normal and hyperplastic growth of the prostate gland. The cancer transformation process involves cellular growth and division. Therefore, an altered endocrine state, such as the suppression of DHT activity, is hypothesized as having a preventive impact on prostate cells on the malignant transformation.¹⁴⁴ Two 5-ARI's have been investigated in randomized clinical trials^{145, 146}. The Prostate Cancer Prevention Trial was initiated in the late 80's in the U.S. by the National Institute of Health¹⁴⁷ in which a total of 18,000 healthy men > 55 years, with a

PSA \leq 3 ng/mL and a normal DRE were randomized to either the 5ARI finasteride (5mg/day) or placebo (one matching tablet per day). After 7 years, a reduction in the period prevalence of end-of-study biopsy-proven PC of 25% was found, in favor of finasteride (the incidence of PC in the finasteride group was 18.4% as compared with 24.4% in the placebo group).¹⁴⁸ However, the initial enthusiasm for finasteride in preventing PC, was dampened by the finding of an increase in the proportion of high grade PCs (Gleason score \geq 7, i.e. poorly differentiated PC, 37.0% in the finasteride group versus 22.2% in the placebo group, $p < 0.001$). In the REDUCE study, focus was on high-risk men, 50-75 years old, with a PSA level between 2.5 – 10 ng/mL and with a previous negative prostate biopsy (6-12 cores).¹⁴⁶ The study revealed a 23% reduced risk of incident biopsy-detected PC with dutasteride as compared to placebo over 4 years (95% confidence interval, 15.2 to 29.8, $p < 0.001$). During the 4 years of the study, 659 of the 3,305 men in the dutasteride group (19.9%) and 858 of the 3,424 men in the placebo group (25.1%) received a PC diagnosis, corresponding to an absolute risk reduction with dutasteride of 5.1%. However, during year 3-4, there was a significant ($p = 0.003$) increase in Gleason score 8-10 tumors (12 in the dutasteride arm versus 1 in the placebo arm).

However, despite indications that 5-ARIs can reduce the incidence of PC, it is not yet known whether these drugs can affect PC mortality (or if they can only cause a delay in PC diagnosis).¹⁴⁹ These medications can also adversely influence sexual function, which needs to be weighed against any potential benefits. The inhibition of the androgen receptors in BPH-cells and PC-cells differs and the biological impact is not fully clear. The impact on the risk of PC of introducing 5ARI's to men who are being regularly screened is unclear. The effect of 5ARI's in men who are already diagnosed with low-risk, localized PC and are managed expectantly (see below) is being investigated.¹⁵⁰

Acetylsalicylic acid and vitamins

Acetylsalicylic acid has been suggested as reducing the risk of being diagnosed with PC. Interests have also been raised in cyclooxygenase inhibitors, especially COX-2-inhibitors. However, an observed increased risk in severe cardiovascular events resulted in that some of these were withdrawn from the market.¹⁵¹⁻¹⁵³

There is some, as yet limited epidemiological evidence that sun exposure and vitamin D reduces the risk of PC.¹⁵⁴⁻¹⁵⁵ Epidemiologic evidence supports the hypothesis that tomatoes (lycopenes),¹⁵⁶ selenium and vitamin E reduce the risk of PC. However, for the latter two, a phase III randomized placebo-controlled trial (SELECT) did not show any preventive effect of supplementation in a generally healthy population and was halted because of concerning trends of paradoxically increased risks of PC in the vitamin E group and type II diabetes mellitus in the selenium group (albeit statistically non-significant).¹⁵⁷ In the Physician's Health Study II, neither vitamin E nor C supplementation reduced the risk of PC¹⁵⁸. Overconsumption of multivitamins may be harmful, increasing the risk of advanced and fatal PC¹⁵⁹.

Diet, physical activity and lifestyle

Some studies indicate that epidemiologic and pathologic links exist between BPH and PC. Recent publications support the hypothesis that both diseases may be part of the metabolic syndrome (a cluster of metabolic disturbances including glucose intolerance/type 2 diabetes, dyslipidaemia, hypertension and central adiposity). Furthermore, inflammation of the prostate is also emerging as contributory to the development of both.¹⁶⁰⁻¹⁶¹ Patients with clinical PC may have the same metabolic abnormality, of a defective insulin-stimulated glucose uptake, and hyperinsulinaemia as patients with the metabolic syndrome.¹⁶² The theory behind this is that hyperinsulinaemia leads to a decreased synthesis of IGFBP-1 in the liver and elevated concentrations of free IGF-1, which can be a potent mitogen of the prostate epithelium. High circulating IGF-I concentrations have been associated with an increased risk of PC in several studies¹⁶³. Hyperinsulinaemia also contributes to higher levels of leptin, and higher serum levels have been associated with the later development of PC¹⁶⁴. Hammarsten et al. have shown that men who died from PC had higher insulin levels than men who were still alive with clinical PC at follow-up. The insulin level has therefore been suggested for use as a marker of PC prognosis and tumor aggressiveness, regardless of the patient's PC stage, cancer grade and PSA level.¹⁶⁵ A diet based on carbohydrates with low glycemic index (GI) and low glycemic load (GL) has been suggested as valuable in the primary prevention of PC since this diet keeps the insulin levels normal; the higher the GI and GL the higher the risk of PC.¹⁶⁶

A high level of physical activity has also been suggested as being associated with a decreased risk of PC¹⁶⁷; however, the epidemiologic evidence is inconsistent¹⁶⁸⁻¹⁶⁹ and the magnitude of the risk reduction observed is small.¹⁷⁰ Smoking is also a suggested risk factor¹⁷¹, although studies diverge.

In a 2009 systematic review of the effect of diet in PC prevention and treatment, the recommended diet is one that is low in fat, high in vegetables and fruits, and avoiding high energy intake, excessive meat, and high dairy products and calcium.¹⁷² In the 2007 report from the World Cancer Research Fund / American Institute for Cancer Research, the panel judged that foods containing lycopene and selenium are probably protective against PC whereas processed meat, milk and dairy products and foods containing calcium are thought to increase the risk. It is unlikely that beta-carotene has an effect on the risk. There is limited evidence suggesting that legumes including soya, foods containing vitamin E, and alpha-tocopherol supplements are protective.¹⁷³

It could be argued that a lifestyle that ensures overall well-being, that is also protective against cardiovascular diseases, overweight, hypertension and diabetes could be advised in the meantime, in the absence of evidence on the true benefits or harms of chemo-preventives and dietary/lifestyle modifications. A Paleolithic diet, i.e. one corresponding to foods that may have been consumed during the Paleolithic Period ('Old Stone Age', between 2,600,000 and 10,000 years ago), has been suggested as being protective against many of the diseases affecting the Western world.¹⁷⁴

1.8. Secondary prevention - possibilities and problems

Since knowledge about the etiology of PC is scarce, there is no given basis for primary prevention. Instead, in theory, the highest chance of successful cure today is through early detection (secondary prevention).

Clinical presentation of prostate cancer

Before the PSA era, PC was usually diagnosed when symptoms of locally advanced, regionally advanced or metastatic disease occurred, or when patients were investigated or treated for what was presumed to be benign disease¹⁷⁵. PC most often grows in the peripheral zone of the prostate, whereas BPH grows in the transitional zone that is adjacent to the urethra, and thus gives lower urinary tract symptoms when the prostate becomes enlarged. Urinary symptoms such as hesitancy, poor stream, nocturia, frequency and urgency result from mechanical obstruction to the bladder outflow. About 80% of prostate tumors originate from the peripheral zone, which is distant from the urethra, and only 15-20% from the peri-urethral, transitional zone¹⁷⁶. Early stage PC is therefore often a silent disease and bladder outflow obstruction a late event. Only 13% of patients with acute urinary retention have underlying PC¹⁷⁷. As the disease progresses, some men can have symptoms such as urinary frequency or poor stream (lower urinary tract symptoms). Advanced PC can invade the urinary bladder, seminal vesicles and rectum and give rise to symptoms such as haematuria, haemospermia, perineal pain and rectal bleeding. Unexpected malaise or unrelenting bone pain in elderly men may suggest signs of metastatic disease.

Metastasized disease is often associated with severe morbidity and can be extremely painful when spread to the bones. Skeletal metastasis may, in the worst case, affect the spinal cord with compression resulting in paralysis of the legs and/or the urinary bladder, which is a feared condition that requires acute intervention. While historically, spinal cord compression was sometimes the first presentation of metastatic malignancy, early detection has made this rare. Today, PC is most often diagnosed early in the course of its natural history, many years before progression to skeletal metastases. The use of PSA has altered the presentation of PC, both of the initial disease state and of recurrent disease after treatment by earlier identification of failure through PSA monitoring.¹⁷⁸

Screening can alter the natural history

Since the window for curative treatment is limited, screening for PC seems intuitively to be beneficial since it provides a way of finding the disease before the cancer cells have reached outside the prostate capsule and started to invade the surrounding tissues or have spread to the lymph nodes or already metastasized.

In its early stage, PC is a silent disease. By the time symptoms become present, the disease is generally more advanced and often the disease is too advanced to cure. This underlines a theoretical importance of screening, since it provides the only way to identify asymptomatic men with PCs that are completely curable. The fact that PC is

possible to treat and cure at an early stage, but impossible to cure when more advanced (although treatment in advanced stages of the disease can also affect prognosis, see below) makes a strong argument for screening. The metastatic status at time of diagnosis has a profound impact on disease-specific survival; men with distant metastases at diagnosis have in general a poor prognosis with a median survival of 2.5 years.¹⁵

Early detection through screening provides an opportunity for curative treatment. The window of curability for PC is markedly decreased when the tumor is already greater than 1.5 cubic centimeter and even a significant level of small volume cancers exhibit extraprostatic extension¹⁷⁹. Results of cancer control ten years after radical prostatectomy provide evidence that disease confined to the prostate is curable¹⁸⁰. PC-specific survival in organ-confined disease has been reported as being 94-98% at 10 years^{85,181}, 82%-90% at 15 years¹⁸²⁻¹⁸³ and 76% at 30 years.¹⁸⁴

High prevalence on autopsy

The prevalence of latent PC is high. We know from autopsy studies that many men, dying from other causes, have cancer cells in their prostate glands. The earliest study from Johns Hopkins Hospital in the U.S., was published by Rich et al. in 1935¹⁸⁵. In 292 consecutive autopsies on males older than 50 years dying from a wide variety of causes, PC was found in 41 cases (14%). In 66% of these cases, the tumors were reported as not having been clinically recognized, but on autopsy, most often found near the outer margins of the prostate gland, and even when only a few millimeters in size, showed a tendency to invade the prostate capsule. Latent PC on post mortem examination has been shown to increase with age and also to vary with geography, with for example a low prevalence in China and a high prevalence in Sweden.¹⁸⁶ More recent studies show a PC occurrence on autopsy of approximately 30-50% in males between 50-70 years¹²⁹ (i.e. those subjected to screening in today's trials). A recent study of incidental PC diagnosed in organ donors found PC in one in three men aged 60-69, and this increased to 46% in men over the age of 70¹⁸⁷.

What cancers are detected by screening?

The high prevalence of latent PC on autopsy and the comparatively "low" incidence of clinical PC pose a risk of over-diagnosis with screening. A screening program risks detecting some PCs that might not be life-threatening, whose carrier would not benefit from treatment, but only suffer from side-effects. With screening, there is also a small risk (although much lower compared to the risk of detecting indolent cancers) of detecting aggressive, previously undetected tumors for which local treatment would be ineffective and curative treatment impossible.

Catalona et al. showed early, in 1993, that PSA screening identifies an increased proportion of organ-confined tumors (clinically localized) as compared to the evaluation for abnormal DREs. The PCs detected with PSA were of intermediate histological grade of tumor differentiation.¹²

Advanced disease is associated with high morbidity

The risk of relapse after initial treatment with curative intent for locally advanced PC¹⁸⁸, together with the morbidity and hospital care costs associated with advanced or metastasized diseases are other incentives for trying to detect PC at an early stage. The morbidity from advanced PC can be devastating for a man. Patients who fail deferred treatment consume a fair amount of health care resources (hospital care and palliative therapy) before they succumb from PC.¹⁸⁹ We know today that PC screening can significantly reduce the absolute risk of being diagnosed with metastatic PC after 10 years of follow-up¹⁰⁸. We also know today that PC is a potentially hazardous disease, and even small tumors will eventually progress to metastatic disease if the patient lives long enough¹⁹⁰. PSA screening can reduce these risks.

1.9. Treatments for prostate cancer

Various treatments for PC are available, either with curative intent or in palliative care depending on PSA level, tumor stage, Gleason score (the pathological grading), patient age, co-morbidities, remaining life-expectancy, symptoms, and other patient factors such as sexual function, anxiety et cetera.

The assessment of the extension of the tumor (staging) is made by DRE, PSA, operative lymphadenectomy and bone scan, with the aid of computed tomography (CT) or magnetic resonance imaging (MRI) and chest X-ray in some situations. The clinical stage of the extent of the cancer spread is described by the TNM-classification;¹⁹¹ T – tumor, N – lymph nodes, M – metastases (table 1). Treatments differ for localized tumors (T1-T2, N0, M0), locally advanced tumors (T3-4, NX-N0, MX-M0), metastasized disease (T1-4, N1 or M1) and castration-resistant tumors.

Table 1. TNM classification of prostate cancer stage⁸⁵

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2	Tumour confined within the prostate ¹
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule ²
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement.
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes ³	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant metastasis ⁴	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Management and curative treatment options include radical prostatectomy (open retropubic, laparoscopic or robot-assisted as well as perineal), radiotherapy (dose-escalated external beam radiotherapy or external beam therapy combined with either high-dose rate brachytherapy or radioactive seeds implantation), watchful waiting (with delayed palliative therapy), or active surveillance (with delayed treatment with curative intent). Early endocrine therapy can be an option for certain patients. Endocrine therapy (in different administrations and combinations with other treatment modalities) is reserved for patients with locally advanced tumors, at recurrence after surgery or radiotherapy and for primary metastasized disease. Postoperative endocrine treatment or radiotherapy can be administered adjuvant to surgery for tumors with positive margins or PSA recurrence. Palliative treatment also includes radiotherapy targeted at skeletal metastases and chemotherapy.⁸⁵

Two different forms of expectant management

PC is almost unique among solid tumors in that a substantial proportion of patients may not need immediate treatment¹⁷⁸. Two forms of management of PC exist that both entail expectation: watchful waiting (WW) and active surveillance (AS). Watchful waiting is a strategy for administering hormonal treatment when local or systemic symptomatic progression occurs, whereas the concept of active surveillance is fundamentally different in that it is a strategy for delivering curative treatment when pre-defined signs of progression occur (i.e. a short PSA doubling time or deterioration of Gleason score at repeat biopsy). Watchful waiting is also known as 'deferred treatment' or 'symptom-guided treatment'. This strategy emerged in the pre-PSA screening era (before 1990); at the time symptoms occurred, the patient would be treated with palliation including TURP or similar for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions. Active surveillance is also known as 'active monitoring'. It is a newer term developed in the past decade and includes an active decision to postpone immediate treatment and closely monitor the patient for signs of progression.⁸⁵ Active surveillance candidates are often healthy and potentially fit for curative treatment while men under watchful waiting are often elderly men or men with co-morbidities and limited life-expectancy. The rationale behind watchful waiting was the observations that PC can progress slowly, and is diagnosed in older men in whom there is a high incidence of co-morbidity and related high competing mortality.⁸⁵

Watchful waiting

Observation emerged as a therapeutic alternative in men with PC and a low risk of disease progression, based on the findings of Chodak et al.¹⁹² and Albertsen et al. (the latter reporting outcomes for men diagnosed in 1971-1984)¹⁹³ that men with favorable PC face a low risk of death from PC within 15 years of follow-up. In the pooled analysis by Chodak et al. of 828 case records from six non-randomized studies (published between 1985-1992) of men treated conservatively (with observation and delayed hormone therapy but no radical surgery or irradiation) for clinically localized PC, the disease-

specific ten year survival was 87% for low grade tumors, but only 34% for grade III (high grade) tumors. The corresponding figures for metastasis-free survival were 81%, 58% and 26% for grade I (low), II (intermediate) and III (high grade) tumors, respectively. These findings correlate with the register study by Lu-Yao et al. from the U.S. Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute. The 10-year disease-specific survival was 92%, 76% and 43% for grade I, II and III tumors, respectively.¹⁹⁴ Early cohort studies by Johansson et al. and Adolfsson et al., with patients diagnosed in the 70's and 80's, indicated a fairly good ten-year natural history of initially untreated early-stage PC (watchful waiting), but with a high risk of death for patients with poorly differentiated tumors.^{34, 195}

The earliest natural history studies for PCs following conservative management by Chodak et al., Albertsen et al., Johansson et al. and Lu-Yao et al. demonstrated 10-year disease-specific survival estimates varying between 48-93% for moderately and well-differentiated tumors whereas the corresponding figure for poorly differentiated tumors is reported to be 23-45%.^{192-194,196} Further follow-up (for initially untreated tumors), between 15-20 years, demonstrated a high risk of dying from the disease for GS 8-10¹⁹⁷ and for all tumors a disease-specific survival decreasing from 78.7% to 54.4% with time.¹⁹⁸ The Albertsen studies show that GS 7-10 tumors carry a continuously increasing risk of ending the patients' lives for up to 15-20 years after conservative management,^{85, 193, 197} even when diagnosed at 74 years of age.¹⁹³

PC is a complex disease with an extraordinarily variable clinical outcome, with a natural history best predicted today by the histological Gleason scoring system, clinical stage and PSA-level at diagnosis. However, given sufficient time, PC is highly likely to progress to systemic disease and death unless there are competing causes of death. Patients with a life expectancy exceeding 10 years have been shown to have a higher mortality rate from PC (localized at diagnosis) when left without curative treatment^{190, 199-200}. In a population-based prospective Swedish study, Aus et al. found a 56% cumulative risk of dying from PC after 15 years of follow-up (in a setting where active screening was not advocated).¹⁹⁹

Active surveillance

The approach using active surveillance was first proposed by Klotz in 2005²⁰¹, as many "good risk patients" were believed to be over treated. Active surveillance can be suitable for men with low risk disease: localized tumors T1c-T2a, Gleason score ≤ 6 and PSA < 10 ng/ml²⁰². Since there seems to be a window of curability for patients with favorable risk disease, radical treatment can be initially withheld, but is still an option over time with this strategy (as opposed to watchful waiting). Patients with clinically low-risk PC under an active surveillance program are, as the name implies, monitored closely under a strict follow-up protocol with repeated PSA measurements and prostate biopsies. They are offered delayed curative treatment when the PC is reclassified as a high-risk tumor over time, based on biochemical or pathologic progression of the disease.

Active surveillance is evolving as a therapeutic strategy with the aim of decreasing the burden of therapy in patients with indolent disease, while providing definitive therapy for those with biologically active disease.²⁰³ The expectations behind active surveillance are to minimize the risk of over treatment of indolent tumors (as with early invasive treatment) and minimize the risk of under treatment of advanced tumors (as with watchful waiting).

Screening for a cancer without offering an active intervention may seem to be a contradiction and to involve an ethical dilemma. However, expectant management with active surveillance is becoming a more commonly used option today. This concept is now being tested in large-scale trials, but this far, only < 10 year data are available.

One of the first large prospective trials was initiated in 1995 by Klotz et al. In a recent report of this cohort of 450 patients, with a median follow-up of 6.8 years (range 1–13 years) overall survival was 78.6% and the 10-year PC actuarial survival was 97.2%. Overall, 30% of patients were reclassified as being at higher risk and were offered definitive therapy. Of 117 patients treated radically, the PSA failure rate was high at 50%.²⁰⁴ This reinforces the importance of close monitoring and of definitive treatment for those in whom disease is reclassified as higher risk over time²⁰⁵.

Results from the ERSPC trial on 616 men diagnosed between 1994 and 2007 (PSA \leq 10 ng/ml, PSA-density \leq 0.2 ng/ml per ml, stage T1c/T2, GS \leq 3+3 = 6, and \leq 2 positive biopsy cores) have shown a calculated 10-year PC-specific survival for men on active surveillance of 100% (median follow-up 3.9 years). The calculated treatment-free survival was low at 43%.²⁰⁶

Receiving a screen-detected PC diagnosis and not electing to have definitive treatment, can be a choice, according to Klotz, based on five postulates²⁰⁷: 1) Screen-detected PC may be clinically insignificant (will not pose a threat to the man's health), 2) Patients selected to active surveillance can be identified with reasonable accuracy, 3) No treatment lacks side-effects, 4) Patients with low risk reclassified as high risk over time can be radically cured in most cases, 5) The psychological burden of living with untreated PC may have less impact on quality of life than early therapy.

Fears have been raised that anxiety will result from a cancer diagnosis and that some men cannot be dissuaded from immediate treatment. However, recent work from North America and the Netherlands suggest that this need not be the case. Burnet et al. concluded that active surveillance for managing localized PC was not associated with greater psychological distress than more immediate treatment.²⁰⁸ van den Bergh et al. showed that men on active surveillance report even favorable levels of anxiety and distress as compared to men who underwent other treatments for localized PC²⁰⁹. Another study suggests no difference in anxiety between active surveillance and radiotherapy²⁰⁸. The ongoing randomized trials worldwide will provide further knowledge on effective treatment options for PC.

Expectant management of PSA-detected tumors

The natural history of today's PCs that are more often PSA-detected is not fully understood. Lead-time bias refers to the time interval by which PC is detected by screening as compared to the clinical detection. It may seem that screening prolongs life, when, in some cases, only the observation time is prolonged. Therefore, comparing survival between screen-detected tumors and clinically detected tumors can be difficult.

In a recent observational study, the National Prostate Cancer Register (NPCR) of Sweden follow-up study, including men aged ≤ 70 at diagnosis, local tumor stage T1-2, NX or N0, MX or M0, and PSA < 20 ng/mL, Stattin et al. reported a cumulative 10-year PC-specific mortality for men with low-risk PC of 2.4% (95% CI = 1.2% to 4.1%) among 1,085 patients on conservative treatment and 0.7% (95% CI = 0.3% to 1.4%) among 1,601 patients who received treatment with curative intent. The 10-year risk of dying from competing causes was 19.2% in the surveillance group and 10.2% in the curative intent group, indicating that patients with a short life expectancy were more often selected for surveillance than for surgery or radiation therapy. Conservative treatment (coded as "expectancy" in NPCR) included both active surveillance and watchful waiting. Another limitation of the study was the median follow-up time of 8.2 years. Many patients currently diagnosed with localized PC at age 60–70 have a life expectancy of more than 15 years. A low 10-year disease-specific mortality of only 3% for surveillance makes this regimen suitable for many men with low-risk disease; however, longer follow-up is awaited.²¹⁰

Radical prostatectomy

The approach of treating PC by means of surgery was first applied by Billroth who performed the first perineal prostatectomy in the 1860's²¹¹ and later by Young in the beginning of the 20th century²¹². Initially, radical prostatectomy (RP) was performed primarily for palliation. In 1931, transurethral prostatic resection became available and was adopted as a palliation for obstructive PC.⁷ The first prostatectomy with a radical retropubic approach was performed by Millin in 1945. However, the procedure was associated with high mortality and morbidity; severe urinary incontinence, erectile dysfunction and stricture of the vesicourethral anastomosis. Many of the tumors were detected at a late stage.²¹³ With the discovery of the PSA, this was dramatically changed when prostatectomy could be regarded as a means of successfully treating PC detected at an early stage. During the 1970's, efforts were initiated to decrease the per- and postoperative complications. In 1982, Walsh described the detailed anatomy of the prostate gland, the dorsal venous complex and the existence and function of the neurovascular bundles²¹⁴. These pioneering efforts helped in modifying the radical retropubic surgical dissection of the prostate²¹⁵ and led to improvements in postoperative continence and potency as well as reducing perioperative mortality. Further modifications and improvements in surgery, anesthesia and pre- and postoperative care have been made throughout the years, with a concomitant decrease in complication rates²¹⁶. RP is the gold standard of treatment for localized PC; however it is not clear

which technique is superior in terms of oncological and functional results and cost-effectiveness⁸⁵. RP can be performed either as open retropubic surgery, laparoscopic or robotic-assisted laparoscopic surgery as well as perineal. Observational studies have compared the outcomes of these modalities²¹⁷, but no RCT exists to date.

Consistent with increased diagnostic activity, especially testing with PSA, the incidence of PC in Sweden has risen rapidly today, as have rates of treatment with curative intent.²¹⁸ In 2006, more than 2,000 radical prostatectomies were performed²¹⁹.

The VACURG study

Early treatment with radical prostatectomy has been evaluated in both RCT's and observational studies. In 1995, Iversen et al. reported on the 23 year follow-up from the Veterans Administration Cooperative Urological Research Group (VACURG), an RCT comparing radical prostatectomy with watchful waiting between 1967 and 1975 in the U.S. However, this study was relatively small (underpowered to detect treatment differences) and vital status was assessable for only 111 of the 142 men. The tumors were classified as clinical stage I or II (clinically localized or locally advanced); however, staging was simplified which could also have affected the outcome. This study could not demonstrate any difference in overall survival.²²⁰

The SPCG-4 study

A decade later, a larger RCT was able to report on the benefits of early treatment. This Scandinavian study (SPCG-4) conducted by Holmberg et al., randomized (in 1989-99) 695 men with clinical stage T1-2 tumors; 348 men to watchful waiting and 347 men to radical prostatectomy. Men in the watchful waiting group received no immediate treatment, but underwent transurethral resection if sign of obstructive symptoms occurred. Both groups received hormonal therapy if metastases were confirmed. The hormonal therapies used were mainly orchiectomy or gonadotropin-releasing hormone analogs as lifelong therapy. During a median of 10.8 years of follow-up, radical prostatectomy significantly reduced the risk of local progression (RR = 0.36, 95% CI 0.27 - 0.47; $P < .001$), the risks of metastasized disease (RR 0.65, 95% CI 0.47 - 0.88; $P = .006$) and disease-specific mortality (RR 0.65, 95% CI = 0.45 - 0.94; $p = 0.03$).¹¹⁴ At a median of 8.2 years of follow-up the difference between the two arms in overall mortality rates was statistically significant²²¹, but not at 10.8 years for all ages – however it was significant for men < 65 years (RR 0.59, 95% CI 0.41 - 0.85, $p=0.004$)¹¹⁴. The results from this landmark study showed that, at 12 years, the absolute reduction in the risk of PC death was somewhat small, 5.4% (12.5% in the surgery group vs. 17.9% in the watchful waiting group had died of PC), however, the reductions in risks of local tumor progression and metastases were larger (19.3% of men in the surgery group vs. 26% of men in the watchful waiting group had been diagnosed with distant metastases).¹¹⁴ The number needed to treat, NNT, to “cure” a single case of PC with radical prostatectomy compared to watchful waiting was calculated at 10-19.

Observational studies

In 2001, Barry et al. reported 10-year survival outcomes in a retrospective cohort study including 2,311 men aged 55-74 diagnosed with non-metastasized PC between 1971-1984 and who were managed with either radical prostatectomy, external beam therapy or observation. Kaplan-Meier estimates for disease-specific and overall survival were in favor of radical prostatectomy (86% for disease-specific mortality, 95% CI, 84-88% and 69% for overall survival, 95% CI, 67-71%) and lowest for men who underwent observation.²²²

In 2006, Wong et al. reported overall and cause-specific mortality results from an observational cohort study (in more than 44,000 men) using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare that compared initial treatment (radiation therapy or radical prostatectomy) with observation in men aged 65-80 with low and intermediate risk localized PC. At 12 years of follow-up, men who received active treatment had statistically significant improvements in overall and PC specific mortality versus men who underwent observation (37% vs. 24% deaths).²²³ However, non-randomized studies should be interpreted with caution, since they can be subjected to selection bias in that men who select these alternative management strategies have different characteristics.

Radiotherapy

Radiation therapy (RT) has been used since the 1960's for the treatment of PC. Modifications throughout the years have been focused on concentrating the radiation energy to the prostate and minimizing the toxicity to the surrounding organs (urinary tract and bowel toxicity).²²⁴ A number of different radiation techniques are available today, including external beam radiation therapy or brachytherapy (high-dose rate brachytherapy or seeds implants). A combination of external beam radiotherapy and high-dose rate brachytherapy seems to provide favorable results as regards biochemical control as compared to external beam radiotherapy alone²²⁵ or in combination with radioactive seed implantation.²²⁶

According to the National Institutes of Health (NIH) consensus, external beam radiotherapy offers similar long-term survival as surgery and equal quality of life.^{85,227}

In 2009, Widmark et al. reported the results from the SPCG-7-study, a randomized trial comparing endocrine therapy with and without local radiotherapy, followed by castration on progression. For men with locally advanced or high-risk local PC (T3; 78%; PSA < 70 ng/ml; N0; M0), the addition of local radiotherapy to endocrine treatment (three months of total androgen blockade followed by continuous endocrine treatment with flutamide) halved the 10-year PC-specific mortality and decreased overall mortality with an acceptable risk of side-effects compared with endocrine treatment alone. The cumulative 10 year prostate-cancer-specific mortality was 23.9% in the endocrine alone group and 11.9% in the endocrine plus radiotherapy group (difference 12.0%, 95% CI 4.9-19.1%).²²⁸

In a meta-analysis of randomized trials, Bria et al. concluded that hormone treatment added to radiotherapy significantly decreases biochemical failure and clinical progression-free survival for men with locally advanced PC.²²⁹

Endocrine therapy

Endocrine therapy is mainly used in patients with advanced PC, incurable disease, in delaying clinical progression and in reducing symptoms in men with metastasized disease. The principle behind this is that the elimination of androgens from the testes has inhibitory effects on PC cells. This elimination can be achieved by means of surgically removing the testes, by inhibiting the gonadotropin secretion from the pituitary gland that normally stimulates the testes (GnRH-agonists or antagonists), or by estrogens reducing the secretion of GnRH from the hypothalamus. Antiandrogens block the effect on the receptor level.

In recent years, early hormonal treatment has been shown to have benefits even at some of the earlier stages of the disease. Messing et al. have shown that immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy improves survival and reduces the risk of recurrence in patients with node-positive PC.²³⁰ For men with locally advanced PC, the study by Bolla et al. in 2002 showed that immediate (early) androgen suppression with a GnRH analogue given during and for 3 years after external beam radiation improves disease-free and overall survival.²³¹

The antiandrogen bicalutamide can be used either as monotherapy or adjuvant to standard therapy. A large randomized trial (SPCG-6) within the Early Prostate Cancer (EPC) program evaluated endocrine therapy with bicalutamide (150 mg/day) in addition to standard care (radiotherapy, radical prostatectomy or watchful waiting; the majority were followed conservatively).²³² For men with locally advanced disease, the study showed that endocrine therapy in addition to standard care improved overall survival, a significant reduction in the risk of death of 35% (HR 0.65; 95% CI 0.50 – 0.85; $p = 0.001$) relative to standard care alone, as well as progression-free survival, a reduction in the risk of progression by 53% (HR 0.65; 95% CI 0.55 – 0.76; $p < 0.001$) compared with standard care alone, after a median of 7.1 years of follow-up. PC mortality was lower in the bicalutamide plus standard care group (25.5% as opposed to 34.8% in the standard care alone group). This was reflected in the overall survival. However, these benefits were not seen in men with localized disease. Instead, primary antiandrogen therapy for localized PC may result in worse outcomes for these patients.

Lu-Yao et al. have reported that patients with localized PC (T1-T2) have a lower 10-year PC-specific survival with primary androgen deprivation therapy compared with conservative management. However, a subgroup of men with poorly differentiated cancer had improved PC-specific survival with the same treatment (but no effect on overall survival).²³³

It thus seems that endocrine therapy should mainly be withheld until there is proof of disease activity, but whether to deliver it before the patient develops metastatic disease is yet uncertain⁸⁵.

Side-effects from treatment

All treatments for PC at different stages have side-effects. Major improvements in curative therapy have been made during the past three decades and the risk of side-effects has fallen. Early invasive therapies with curative intent seem to offer equivalent tumor control, but the spectrum of acute and late side-effects differs¹⁷⁸. Today, radical prostatectomy is a less invasive procedure with lower morbidity, providing good control of clinically localized PC and with a 10-year PC-specific survival rate of 95%.¹⁸¹ The main side-effects include erectile dysfunction, urinary incontinence and a lesser risk of stricture of the vesico-urethral anastomosis²³⁴. However, some men can have erections with medications such as oral PDE5-inhibitors or intra cavernosal, or intra urethral injections. Men reporting severe incontinence are few, but complete urinary leakage can adversely and tremendously affect a patient's quality of life. In the most severe cases, this condition needs surgical implantation of an artificial sphincter or other strategies.

Side-effects from radiotherapy include erectile dysfunction, increased frequency of micturition, urge urinary incontinence, strictures and bowel disturbances (diarrhea, rectal bleeding or fistulae). Long-term side-effects include secondary cancers (bladder and rectal), hip fractures as well as proctitis and post-radiation hemorrhagic cystitis which may have a huge negative impact on the patient's quality of life.

The most bothersome permanent side-effects after radical prostatectomy are urinary incontinence and erectile dysfunction²³⁵. In reviews, the incidence of post-prostatectomy potency rates has varied between 11%-87%²³⁶⁻²³⁷ and post-prostatectomy incontinence between 0%-87%²³⁶⁻²⁴⁰. At 52 months after radical prostatectomy, 88% have been reported to suffer from erectile dysfunction and 31% from urinary leakage, while the corresponding figures for external beam radiotherapy is 64% and 13%, respectively, and in the latter group there is also a marked effect on bowel function and bowel bother scores.²⁴¹ Long-term PC survivors have reported even better health-related quality of life (HRQL) scores compared with a control group of men without cancer (radical prostatectomy patients had the highest HRQL, followed by watchful waiting, radiotherapy and with the lowest scores for patients receiving hormonal treatment).²⁴²

Adjuvant hormone therapy is reported to be associated with worse outcomes across multiple quality of life domains among patients receiving brachy- or radiotherapy.²⁴³ For hormone therapy, there are, unfortunately, many side-effects. GnRH agonists are associated with loss of potency and libido, nausea and vomiting, hot flushes, weight gain, osteoporosis, energy loss and mental disturbances. GnRH agonist treatment is preceded by a couple of weeks of antiandrogens to avoid the initial "flare up", an increase in testosterone levels and risk of deterioration of the disease. In patients with advanced disease, the surge in testosterone can lead to flare-up of tumor growth that can cause urethral obstruction, bone pain and spinal cord compression. Antiandrogens can be combined with GnRH agonists (total androgen blockade) or orchiectomy, or can be given as monotherapy. The main side-effects associated with antiandrogens are the risk of gynecomastia (breast development) and breast tenderness or pain. A single dose prophylactic radiotherapy of the breast can decrease these risks.²⁴⁴

1.10. The WHO-criteria for introducing screening

In 1968, ten criteria were set up by Wilson and Jungner, on behalf of the WHO, that need to be met to justify population-based screening for any disease, in general:²⁴⁵⁻²⁴⁶

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognizable disease.
3. Facilities for treatment and diagnosis should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Notably, evidence from randomized screening studies was not part of these criteria. Nor were ethical issues such as over-diagnosis and over treatment discussed. A review exploring these ten criteria was published by Postma and Schröder in 2005.¹⁰⁷

1.10.1. Criterion 1 – An important health problem

"The condition sought should be an important health problem."

In Sweden, PC is the most common cancer form in men and also the most common cause of cancer-related death in men¹⁰. Approximately 5-6% of all men who die each year in Sweden succumb to PC. Every year, 2,500 men die of the disease in Sweden (as compared to 1,500 women dying from breast cancer and 500 people dying in traffic accidents). There is no doubt about the importance of this disease. Advanced PC is associated with low quality of life and expensive health care, even among elderly men. The fact that PC is a major health problem, associated with significant morbidity and mortality satisfies the first criterion for mass screening.

1.10.2. Criterion 2 – Treatment and side-effects

"There should be an accepted treatment for patients with recognizable disease."

As illustrated in the previous section (see 1.9.), the summary of evidence clearly indicates the advantages of early treatment in all stages of the disease: for localized, locally advanced, and metastasized disease. Complications from the various treatments

are also dependent on the stage of the disease. The SPCG-4 study demonstrated a significant effect on overall mortality at 10.8 years for men < 65 years with localized PC in favor of radical prostatectomy.¹¹⁴ Although this study was very well carried out, it is unclear whether these results can apply to today's Western male populations, who are diagnosed more often by PSA testing contrary to the population in this study (in which only 5.2% were screen-detected tumors and 74-78% of tumors were T2, i.e. palpable).

The effect on screen-detected tumors remains to be established from ongoing trials. An RCT began in 1994 and is addressed at comparing radical prostatectomy with watchful waiting for clinically localized PC (stage T1-2), as in SPCG-4, but of which 75% were detected by PSA elevation or rise: the U.S. Prostatectomy Intervention Versus Observation Trial.²⁴⁷ The Prostate Testing for Cancer and Treatment began in 2001 and is a 3 arm RCT in the U.K. comparing radical prostatectomy with external beam radiotherapy or active surveillance for clinically localized PC detected through PSA testing.²⁴⁸ The Standard Treatment Against Restricted Treatment (START), lead by the National Cancer Institute of Canada, enrolls men in Canada, the U.S. and the U.K., and will compare early interventions, determined by patient or provider preference to active surveillance with delayed intervention.²⁰² SPCG-4 was the first RCT that assessed long-term outcomes of modern PC care. PIVOT will soon contribute information in men with PC detected early in the PSA era. ProtecT and START will increase this knowledge for men diagnosed later in the PSA era and investigate active surveillance regimens. Or as expressed by Wilt in 2008: "The SPCG-4 provided a needed START to PIVOTal data to promote and ProtecT evidence-based PC care."²⁴⁹

Studies assessing the side-effects from treating screen-detected as opposed to clinically diagnosed tumors are also called for.

1.10.3. Criterion 3 – Facilities

"Facilities for treatment and diagnosis should be available."

At present, resources for general screening ("screening clinics" including the complete "urological arsenal") are not available in Sweden, not even in the major cities. Whether enough facilities for treatment/management of men with screen-detected PCs in a situation in which more men undergo screening is already available (pathologists, urologists, oncologists, nurses et cetera) is difficult to estimate today.

1.10.4. Criterion 4 – Latency

"There should be a recognizable latent or early asymptomatic stage."

From autopsy studies, we know that there is no doubt about the existence of a latent stage (see above). Almost 30-50% of men in the 5th to 7th decade harbor cancer cells in their prostate glands¹²⁹. PC most often has a long preclinical stage; a prerequisite that optimizes the detection of the cancer long before signs of symptoms. The potential of finding PCs at an early stage, while they are still curable, has proved to be highly efficient with PC screening²⁵⁰. Results from the Göteborg randomized population-based PC screening trial show that with 10 years of follow-up, the risk of being diagnosed with metastatic PC is reduced by 48.9% (decreasing from 47 cases in the control group to 24 cases in the group randomized to screening).¹⁰⁸ However, the fact that PC can have a long latent stage is also associated with a risk of over-diagnosis, which in turn can entail a risk of over-treatment.²⁵¹

1.10.5. Criterion 5 – Test

“There should be a suitable test or examination.”

The ideal screening test should be available, acceptable, minimally-invasive, accurate and affect the outcome of the disease⁸. However, no such diagnostic test exists today.

The ability to find a cancer through a simple blood test is a remarkable achievement, in itself, and the PSA test is probably one of the most accurate screening tools that exists today. Today, PSA is one of the best and most frequently used tumor markers. PSA in combination with digital rectal examination, i.e. palpation of the prostate and transrectal ultrasound (TRUS) with prostate needle biopsies, give a high number of detected PCs. Although the specificity and sensitivity of the modalities are good, but not ideal (see above), repeat screening with PSA is sufficient to find most early cancers while they are still curable²⁵⁰. TRUS guided prostate biopsy is nowadays the gold standard for the diagnosis of PC. The suspicion of PC is usually raised in connection with an elevated PSA or an abnormal digital rectal examination, which both have a rather low specificity.⁸⁸ The positive predictive value in the ERSPC study is reported to be 24% (i.e. the proportion of men with a ‘positive’ test result who actually have the disease).^{39, 66} The PSA test is a simple and inexpensive diagnostic test. It also has the sensitivity to diagnose PC (with repeated testing) before symptoms with almost 99%.^{250, 252}

1.10.6. Criterion 6 – Acceptability

“The test should be acceptable to the population.”

PSA is a simple and safe blood-test, acceptable to almost any man. The PSA test and the DRE take only a few minutes to perform, and involve minimal discomfort. In the PLCO study, DRE was rarely associated with pain or bleeding (0.3 per 10,000 screened). The

PSA blood test was associated with dizziness, bruising and hematoma in 26 per 10,000 screened and fainting in 3 per 10,000 screened. Although the TRUS-guided prostate biopsy procedure itself is considered unpleasant by some men, the majority of screened men with a positive screening test regard it as acceptable²⁵³ and are willing to undergo a repeated biopsy if needed²⁵⁴. In the PLCO, complications from prostate biopsies included infection, bleeding, clot formation and urinary difficulties in 68 per 10,000 diagnostic evaluations.⁴⁰

1.10.7. Criterion 7 – Natural course

“The natural history of the condition, including development from latent to declared disease, should be adequately understood.”

As indicated in the previous section (1.9.) current knowledge of the natural history of PC is limited to clinically diagnosed cases, whilst little is known about the natural history of screen-detected PCs. We do not yet know how many screen-detected PCs might have caused death if left undiagnosed and untreated. In a recent observational study, Stattin et al. reported a cumulative 10-year PC-specific mortality of 2.4% for men with low-risk PC (local stage T1a, b, or c and GS 2-6 or World Health Organization grade I-II and a PSA level <10 ng/mL) on expectant management (as compared to 0.7% for men with low-risk PC treated with radical prostatectomy or radiotherapy).²¹⁰

1.10.8. Criterion 8 – Whom to treat

“There should be an agreed policy on whom to treat as patients.”

There are various forms of treatment for PC depending on a number of patient-related and tumor-related factors, including patient age and tumor characteristics (see above). Level 1 evidence exists for some strategies, although outcomes for screen-detected tumors are fewer. Active surveillance for favorable-risk tumors is being evaluated. It is hoped that major randomized trials (apart from the ERSPC and PLCO) will provide more evidence on treatment options for screen-detected PC (see above). There is no consensus on whether there is a group with very small lesions that do not need at least immediate treatment. The optimal time for when men with early screen-detected PC should be treated to provide a balance between curability and overtreatment is not established.

1.10.9. Criterion 9 – Costs

“The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.”

Results from Norrköping and Göteborg show acceptable costs for a screening program for PC. Sennfält calculated that the economic consequences of implementing a nationwide PC screening program in Sweden would mean additional costs (added to the health care costs for PC) of approximately 30%. Sennfält also calculated that a PC screening program could be regarded as cost-effective if potentially curable PC patients would gain at least one year of survival in good health.²⁵⁵ Cost-benefit and cost-effectiveness calculations are under way within the ERSPC.

1.10.10. Criterion 10 – Case-finding

“Case-finding should be a continuing process and not a ‘once and for all’ project.”

After a mean follow-up of 8.8 years, the ERSPC trial showed a 20% reduction in PC mortality in the core age group of men aged 55 to 69³⁹. Repeated PC screening (‘a continuing process’) is currently favored over a once-only screening (‘once and for all’). However, the optimal screening algorithm and screening interval remain to be decided. There is also a lack of knowledge about which age to start and which age to stop.

1.10.11. Conclusions on the ten WHO-criteria

To sum up, when examining the ten criteria put forward by Wilson and Jungner, we can conclude that the majority of the requirements are fulfilled today. The sum of evidence for introducing screening for PC is not weaker than the evidence for screening for breast cancer with mammography.

- There is no doubt that PC is an important major public health problem (criterion 1).
- Effective treatments are available (criterion 2) and early treatment seems more beneficial than delayed treatment at all stages of the disease; however, none are free of side-effects.
- Resources for a nationwide screening are unavailable today (criterion 3).
- There is undoubtedly a latent stage of the disease (criterion 4). Although PC screening introduces a beneficial stage migration, it may also increase the incidence of non-significant tumors.
- The PSA test is a suitable screening test for PC (criterion 5). Although it has a non-optimal specificity, it is probably the most accurate PC screening test currently

available. The ideal test would be such that it could distinguish between significant and non-significant PC¹⁰⁷.

- The screening procedures, with DRE, the PSA test and TRUS-guided prostate biopsies in screen-positive subjects, are acceptable to the general male population. Complications connected with the procedures are limited (criterion 6).
- The understanding of the natural history of screen-detected PC is not fully known today (criterion 7).
- There is a policy, albeit somewhat controversial, of whom to treat as patients. Research is being continuously conducted on this issue, especially on early, screen-detected PCs (criterion 8).
- The costs of a screening program could be acceptable (criterion 9); however, cost-effectiveness calculations are under way.
- Current evidence suggests that case-finding should be a continuing process rather than a 'once and for all'/'one single screening' project. Repeated PC screening is currently favored (criterion 10), however the optimal interval/algorithm remains to be established.

However, although these criteria are still regarded as 'classics', they may not be fully applicable to today's health care²⁵⁶. However, Wilson and Jungner never expected their criteria to remain unchanged over time: "If anywhere we have appeared dogmatic, we hope this may serve to stimulate discussion, since, in the end, real development depends on an exchange of views."²⁵⁶

In 2008, Andermann et al. made a synthesis of emerging screening criteria proposed over the past 40 years that resulted in the following ten criteria:

1. The screening program should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening-program effectiveness.
5. The program should integrate education, testing, clinical services and program management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The program should ensure informed choice, confidentiality and respect for autonomy.
8. The program should promote equity and access to screening for the entire target population.
9. Program evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

These modern criteria for early detection thus focus more on positive health outcomes balanced against side-effects and potential negative aspects, as well as taking into account equality issues, informed choice and the respect of each individual's autonomy and freedom to make choices about participation. Using these newer criteria, it is still unknown whether the overall benefits outweigh the harms. Cost-benefit and cost-effectiveness analyses are under way. The potential negative and ethical aspects of PC screening need to be taken into consideration.

1.11. Other cancer screening programs

Cervical cancer screening

Globally, cervical cancer is a common disease and a common cause of cancer-related death among females. In the 1950's, cervical cancer was a common female cancer also in Sweden, but with the introduction of an organized, nationwide cytological Papanicolaou (Pap) smear²⁵⁷ screening program in the 1960's, the incidence rate of invasive cervical cancer declined, as did disease-specific mortality. Between 1965- 1982, cervical cancer mortality fell by 34%.²⁵⁸ Today, although never examined in a randomized controlled trial but based on solid evidence from observational studies, regular screening with the Pap test markedly reduces mortality from cervical cancer by 80%.²⁵⁹ However, this screening is also associated with harms, false-positives, additional diagnostic procedures and treatment for low-grade squamous intraepithelial lesions (LSIL), which in turn can have long-term consequences for fertility, pregnancy and sexual quality of life. Two vaccines against the most common human papilloma virus strains (that cause the majority of cervical cancer cases) have recently (in 2006 and 2007) been developed for primary prevention, targeted at young girls (10-12 years) and subsidized by the Swedish government.²⁵⁹

Breast cancer screening

Breast cancer today is the most common cancer form among Swedish women and the second leading cause of cancer-related death among Swedish women after lung cancer⁴. Each year, approximately 7,000 women get the diagnosis and 1,500 die from the disease in Sweden¹⁰. To date, a variety of estimates of the benefits and harms of mammography screening for breast cancer around the world have been published. The most reliable results come from RCT's, many of which have been carried out in Sweden.

In 1977, a trial to investigate the efficacy of mass screening with single-view mammography was established, the so-called *WE-study* ("Östergötland/Kopparbergs-studien"). The study included over 130,000 women aged 40-74. With a follow-up to the end of 1984, it showed a 31% reduction in breast cancer mortality and a reduction in more advanced breast cancers in the screening group.²⁶⁰ Therefore, in early 1985 when these results were published, the National Board of Health and Welfare in Sweden drew up guidelines for general screening with mammography. At that time, a few other studies existed indicating a benefit from mammography screening.²⁶¹⁻²⁶³ A survey of five of the early randomized mammography screening trials in Sweden was presented in 1993 by Nyström et al., including over 270,000 women in total. The estimated reduction of breast cancer related mortality was 24% among those invited to mammography screening. The largest reduction in breast-cancer mortality (29%) was seen in the age group between 50-69 at randomization, whereas among women in the oldest age group between 70-74 screening seemed to have only a marginal impact.²⁶⁴

The scientific basis for the decision-making at that time was not stronger than the evidence is for PC screening today. Gradually, screening was established throughout

Sweden and became nationwide in 1997. Later, the reduction in breast cancer mortality seen in the W-E trial has been shown to remain consistent over long-term follow-up²⁶⁵.

In a review of eight randomized trials of mammography screening conducted up to 2004, Smith et al. concluded that the trials provided conclusive evidence that the policy of offering screening was associated with a significant and substantial reduction in breast cancer mortality²⁶⁶. With thirty years of experience of mammography screening, Tabar et al. reported that randomized controlled mammography screening trials have unequivocally demonstrated prevented death from the disease.²⁶⁷ Duffy et al. have also demonstrated that the majority of breast cancer mortality reduction is due to screening²⁶⁸. However, other authors are somewhat skeptical. In a Cochrane review from 2009, exploring the past two decades of RCTs comparing mammography screening with no screening, Gøtzsche et al. concluded that mammography screening does reduce breast cancer mortality (the RR for seven of the trials combined was 0.81, 95% CI 0.74 to 0.87)²⁶⁹; however, the authors considered that the question whether screening does more good than harm could still be discussed and that the reduction in disease-specific mortality might be small. The main disagreements were due to study-design issues and negative side-effects such as false positives, over-diagnosis (estimated at approximately 30%) and over treatment with effects on quality of life. In earlier publications, Gøtzsche and Olsen criticized mammography screening²⁷⁰⁻²⁷¹. However, in an extensive review by Freedman et al. it was claimed that positive studies on mammography were excluded by the authors simply through misreading of the data and the literature.²⁷²

The benefits of any cancer screening need to be weighed against the potential negative aspects. For breast cancer screening, pain during the procedures is common but brief and not a barrier to screening. Anxiety, distress and other psychosocial effects have been reported as being transient in systematic reviews²⁷³⁻²⁷⁴. False-positive results are common; younger women have more false-positive mammography results, but rates of biopsy are lower. Rates of over-diagnosis are estimated at 1-10% (in the Cochrane review to 30%). Evidence supports a relationship between radiation exposure and breast cancer with much higher doses of radiation than obtained through screening.²⁷⁵

A systematic review of mammography screening from 2007 by Armstrong et al. demonstrated a reduction in breast cancer mortality, an increased risk of mastectomy but a decreased risk for adjuvant chemotherapy and hormone therapy, and only a small effect on psychological health due to false-positive results. However, this meta-analysis also indicated that among women of 40-49 the risks of mammography screening may outweigh the benefits. While screening may decrease a woman's risk of death due to breast cancer, it will, at the same time increase her risks of undergoing unnecessary procedures, breast cancer-related anxiety, discomfort at the time of screening, and exposure to low-dose radiation. The incidence of breast cancer and the effectiveness of mammography may be lower in women in their 40's. This results in less absolute benefit and greater absolute risk than for an older woman. The authors therefore concluded that a woman of 40-49 who has a lower-than-average risk of breast cancer and higher-than-average concerns about false-positive results might reasonably delay screening.²⁷⁶

In comparison to the feared risk of over-diagnosis of indolent PCs with screening based on autopsy studies where microscopic lesions are highly prevalent, the prevalence of breast cancer (and ductal carcinoma in situ) on autopsy has been reported as very similar to those of PC; 39% of women aged 20-54.²⁷⁷

Comparisons of number needed to screen and diagnose in other cancer screening programs

Instead of evaluating relative risks or absolute risks from screening trials for various cancer diseases, more interpretable measures such as the number needed to screen (NNS) and the number needed to treat (NNT) to prevent one disease-specific death can be calculated. The NNT, as developed by Cook and Sackett in 1995, can be expressed as the reciprocal of the absolute risk reduction, ARR (from the intention-to-treat analysis)²⁷⁸. As reported by Rembold in 1998, the NNS is calculated in the same way (1/ARR)²⁷⁹ and corresponds to number needed to *invite* to the screening arm. The NNT is then derived from the excess disease incidence detected by screening. In PC screening, many men with the disease are, in fact, not *treated*, but rather managed. The NNT therefore rather represents the number needed to *diagnose*.

With 9 years of PC screening in the ERSPC, the relative risk reduction in PC mortality was 20%, corresponding to a NNS to prevent one PC death of 1408 (or 1410) and a NNT of 48.³⁹ These results can be compared with those of screening for breast and colorectal cancer. The relative risk reduction among eight randomized trials of mammography has varied from -2% to 42%,²⁸⁰⁻²⁸⁷ and in the Cochrane review, it was calculated as 19%.²⁶⁹ In the 2009 Cochrane review, Gotzsche et al. estimated the summarized relative risk reduction in breast cancer mortality as being 19%, but assumed that the true reduction would only be 15%. Under this assumption, the death rate in the control group was applied to a study group of the same size to estimate the NNS. The NNT was based on the assumption of a 30% level of overdiagnosis.²⁶⁹ In this review, encompassing seven out of eight randomized trials of mammography, the NNS was 2,000 and the NNT was 10 throughout 10 years.^{269,280-287} In a meta-analysis from 2002 including eight randomized breast cancer screening trials with mammography, the summary relative risk reduction was 16% for women aged 39-74, equivalent to a number needed to invite to screening to prevent one breast cancer death of 1,224 (credible interval 665 – 2,654) an average of 14 years after study entry.²⁸⁸ In a recent update of this evidence, the number needed to invite to screening ranged between 377 (CrI, 230 – 1050) for women aged 60-69 and 1,904 (CrI, 929 – 6378) for women aged 39-49 years. The relative risk reduction was estimated as ranging between 15% and 32% for women aged 39-69.²⁷⁵

For colorectal cancer screening by fecal occult blood test, the relative risk reduction has varied between 13 and 33% among four randomized trials²⁸⁹⁻²⁹² and was 16% overall in a 2008 Cochrane review²⁹³ (after 11.7 to 18 years) and in a meta-analysis (after 7.8 to 13 years).²⁹⁴ The NNS after 10 years was estimated as 1,173 (95% CI 741 to 2807). NNT is not estimable since screening may reduce the incidence of colorectal cancer (by means of removing precursors to cancers, i.e. colorectal polyps).²⁹⁵ No subgroup analyses of NNS/NNT per age groups have been reported.

2. ETHICAL ANALYSIS

Screening for PC leaves many dimensions unexplored and available for ethical reasoning. *Even though* we are provided with evidence that mortality from the disease is reduced with screening³⁹, the ethical discussion is quite essential.

When considering a population-based voluntary screening for healthy men, there is an ethical obligation to ensure that it must not cause more harm than good.²⁹⁶ Firstly, the screening programs must take into account the participants' tolerance of the methods used and limit the various risks of morbidity and even mortality that might follow adherence. Secondly, the risks of over-diagnosis and the associated aspects of quality of life (QoL) need further quantifications and interpretations. Thirdly, when there is an increased detection of early PC with screening, there is also an urgent need to evaluate the potentially negative side-effects following treatment. Minimization of postoperative morbidity is of great importance. Fourthly, cost-effectiveness analyses together with considerations on implementation into clinical routine practice must be evaluated.

The ethical issues in PC screening are manifold and some are explored in the papers outlined in this thesis. It is important to understand these issues in order to maximize benefits and minimize harm to the enormous group of men worldwide at risk of this common disease.⁸

2.1. Frameworks for ethical analysis

In medicine and public health, there are many methods for ethical analysis; however, no matter what personal philosophy, politics, religion or moral philosophies one relies on, some principles are often applicable to almost any moral issue.²⁹⁷ In this part of the thesis, two frameworks are presented that will constitute the basis for an ethical analysis. A synthesis of these two is made (independently by S. Carlsson, spring, 2010), very similar to that proposed by Nilstun (Professor in Medical Ethics, University of Lund) et al. in 2009.²⁹⁸

The first framework is a cluster of four moral principles, namely "principlism" or "the four-principle approach", and was presented by Beauchamp and Childress at the Appleton Consensus Conference in 1988²⁹⁹. These are: (1) *respect for autonomy*, (2) *non-maleficence*, (3) *beneficence* and (4) *justice*. Although this approach is not aimed at providing a definitive answer or the solution to a moral issue, it is a helpful means of structuring an ethical analysis. Most classical ethical theories include these principles in some form, and they have long played a central role in medical ethics. PC screening has previously been evaluated by means of these four principles, by Krantz et al. in 2005³⁰⁰. However, the analysis made in this thesis is different.

The second framework was set up by Roberts and Reich in *The Lancet* in 2002 and distinguishes three philosophical views that may be used as tools in analyzing ethical dilemmas in public health:³⁰¹ (1) *utilitarianism*, a position based on outcomes, i.e. decisions should be judged by their consequences, in particular by their effect on the

sum total of individual wellbeing, (2) *liberalism*, a position focused on rights and opportunities and (3), *communitarianism* (not to be confused with ‘communism’), a position that emphasizes the balance between individual rights and interests with that of the community. In discussing the launching of a screening program for PC, the type of ethical choice will vary depending on the framework motivating the decision.

If we link these two frameworks, we find that *respect for autonomy*, *liberalism* and *justice* are closely related. Likewise, *beneficence* together with *non-maleficence* is connected to *utilitarianism* (“the greatest happiness of the greatest number”). *Communitarianism* is presented separately.

2.1.1. Autonomy, liberalism and justice

The philosophical concept of autonomy is associated with the philosopher Immanuel Kant (1724-1804), who is also associated with the moral philosophy of liberalism, a 19th century doctrine rooted in the Enlightenment. The concept refers to the right of an individual to make an informed, un-coerced decision (the right to self-determination in moral choices). All humans are believed to have an ethical obligation to respect each others’ right to self-determination, as long as it does not trespass on others’ rights to self-determination.²⁹⁸ The most recent American philosopher associated with this doctrine is John Rawls (1921-2002). Liberalism prioritizes individual rights and the right to choose. Along these lines, individuals should have positive rights to health, which may include screening for diseases. Liberals who see health as a state-guaranteed right would move to “aggressive” efforts to control certain diseases to improve health outcomes.

With the evidence available today, 2010, an ethical dilemma arises when a man consults his doctor about the PSA test. On the one hand, he should have a right to make his own decisions, provided he receives relevant information. But, how will he be able to judge between pros and cons, when evidence or knowledge is (still somewhat) deficient?³⁰⁰

Although the ERSPC has provided evidence that mortality from PC is reduced³⁹, general PSA screening, either voluntary or “mandatory” (*here*: strongly recommended or encouraged), has not yet been regarded as justified in order to protect the public health since the final conclusive reports on harms and costs are still awaited. These are ongoing within the ERSPC.

From an autonomy point of view, men’s right to self-determination might be regarded as being put aside when general PSA testing is *not* offered. On the other hand, men’s right to self-determination might also be regarded as being put aside *if* PSA testing were being implemented as “mandatory” (*here*: strongly recommended or encouraged) by a government (or similar). Voluntary universal screening rests on encouragement rather than coercion. Such a screening regimen would therefore not violate any moral rights to privacy or autonomy. It is highly unlikely that any government would force a man to take his PSA, but a screening program introduced by a government (or similar) would probably function, at least to some extent, in that

direction. If a man receives a brown envelope with an appointment for screening, like the one women get for breast cancer and cervical cancer screening, many men would probably interpret this as that something good is being done for them. However, the potential negative consequences that might arise from what at first could be regarded as a simple PSA test may not be in the individual man's best interest.

In Sweden, there is now a compromise situation in the medical community that any man requesting the PSA test should be fully informed of its consequences. Fully *informed* men should be free to exercise their personal preferences regarding the test. In April 2007, the National Board of Health and Welfare published National guidelines on PC care and provided a patient brochure⁹ (which was up-dated in April 2010). Before a man takes the PSA test, it is recommended that he reads this written information on the potential consequences the different outcomes of the test might have. The brochure is distributed mainly to primary care or private health care. Discussion with a doctor is thought to be a necessary complement to the brochure.³⁰² From these guidelines, it is concluded that a man may have the PSA test as soon as he is acquainted with the contents of this information about it. Hence the interpretation of these guidelines is that today, no man in Sweden – after receiving information – can be denied the test. In fact, the pattern of PSA use has changed in recent years. Bratt et al. have recently estimated, in a population-based study, that about one third of all Swedish men aged 50 to 75 had a PSA test between 2000 and 2007³⁰³.

The guidelines from the National Board of Health and Welfare thus emphasize the importance of information to men who ask for PSA testing. The American Cancer Society (ACS) and American Urological Association (AUA) write: "Information should be provided to men about the benefits and limitations of testing so that an informed decision about testing can be made with the clinician's assistance." However, as the situation is today, without screening, there is a risk that only (well-) educated, well-informed men ask for the PSA test. Is this ethically justifiable? Or could this even be regarded as an expression of social bias?

In *A theory of justice* (1971) Rawls presented a general concept of justice on how a just/fair society should be built up: "All social primary goods – liberty and opportunity, income and wealth, and the bases of self-respect – are to be distributed equally, unless an unequal distribution of any of all of these goods is to the advantage of the least favored (from a lifetime perspective)". In line with this theory, one could argue that all men, not only the well-informed, should be given the opportunity to choose freely whether to be screened or not.

Allowing men to choose freely is in complete harmony with the principle of autonomy. For these men, voluntary screening (or offering of screening) is preferable. However, while an autonomous choice means the right to choose, it does not have to mean a *duty* to choose, as some individuals prefer paternalism ("The doctors know what is best for me"). For these men, either *no* screening or voluntary screening/offering of screening would be preferable.

Kant argued that individuals ought to be treated with respect, as ends in themselves, and not as means to other individuals' ends. This view directly opposes utilitarianism's (see below) willingness to treat some people as means to others' ends to maximize utility and produce the greatest good for the greatest number. If the number needed to screen and treat to prevent one PC related death is high, the standpoint of liberalism would be critical to implementing nationwide population-based screening programs. Therefore, if screening is beneficial only for a few, other men are treated as means to those men's ends who benefit from screening, which would be in conflict with liberalism.

In Sweden, priorities in health care are often made from the principles of social solidarity and needs. Resources should be spent where needs are highest and with priority for those with severe diseases and poor quality of life. Priorities should also take account of those who are worst-off (solidarity) assuming that all individuals are equal.

On the public health level, resources should be used fairly and rationally for all diseases. Hence screening could be regarded as a priority-setting dilemma in the context of the distribution of scarce resources. Budget constraints often determine the provision of health care services. In its advanced stages, PC is associated with tremendous morbidity, with loss of quality of life and large consumption of health care resources. In health care, the benefits, risks and costs need to be distributed fairly (distributive justice). Would it be fair to bestow resources on Swedish men between 50 and 70 years for PC screening, while other important diagnoses are not allocated money because of restricted health care resources? Would it even be a signal of social bias? Health-care economists would argue that working years lost and contributions to society are more important factors in these calculations than extending life or minimizing morbidity for elderly men. And what would be the cost for management/treatment of early detected disease as opposed to palliative care? Or should the public health burden of PC be regarded as so substantial that a screening program would be justifiable?

Liberalism views the right to health from a lifetime perspective. Would this rather indicate distributing health care resources not on men between 50-70 years but on the younger part of the population? The right to a minimum level of health is mainly regarded as necessary for people in order to have a range of opportunity when they make life choices. Some have therefore argued that the health care system should place priority on averting premature deaths and spend less time on extending the life of the elderly, who have already had a chance to develop and implement their life plans.³⁰¹ But is elderly men's health not important?

In Sweden, women are regularly screened for two major cancer forms, breast cancer and cervical cancer. Despite the fact that more men die from PC than women from breast and cervical cancer together each year⁴ (Figure 7), is PC screening not recommended. Although the diseases are biologically different, affect individuals of different ages, are associated with different morbidity and mortality at various stages of the disease and following treatments – one could argue that the total burden of PC should be regarded as being at least as important and one could indeed discuss the matter from a gender perspective.

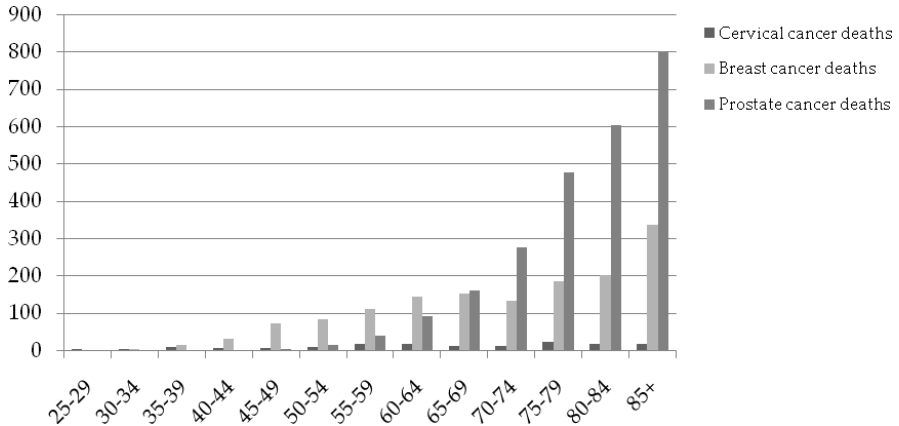


Figure 7. Number of cervical cancer deaths, breast cancer deaths (women only) and prostate cancer deaths per age span, in Sweden, in 2007.
 Graphical illustration: S Carlsson. Courtesy to Socialstyrelsen (National Board of Health and Welfare).⁴

To screen or not to screen?

One difficulty in interpreting results from population-based data, is how they should be translated to the individual level. This is often an impossible challenge. While a reduced disease-specific mortality may be seen for a population, the individual man may not derive any advantages from screening, but only suffer from side-effects (see also below).

Imagine a situation where a man can choose whether to know or not to know about his disease, or to paraphrase Shakespeare's line in *Hamlet*, "to screen or not to screen"; see also front cover of this thesis. Would this man's quality of life be better if he was unaware of the diagnosis? He would continue to lead his life unaware that a tumor was slowly growing in his prostate gland (one day giving rise to symptoms and even death, or perhaps without him ever experiencing any symptoms during his remaining lifetime). Or could early detection through screening, with concomitant early treatment at a curative stage, have prevented the same man from dying too early from the disease? Denying examination and treatment to men who actually have cancers that will be lethal, is to judge an unpredictable group of men to an early, and sometimes severe death. Who decides over humanity, one's right to live?

Anxiety and worry about PC is a common reason for a man to seek a urologist. A normal PSA value might reduce distress. Some men feel that "knowing is better than not knowing". Having the test can provide a man with a certain amount of reassurance – either he doesn't have PC, or he does have it and can have it successfully cured. A psychological benefit is suggested by the fact that PC screening has some reassurance value for 97% of men.³⁰⁴ Some men have a philosophy of life that makes them grasp any opportunity to avoid a serious cancer disease later in life. Other men value their current quality of life higher, especially if they are afraid of side-effects from early treatment with curative intent (impotence, urinary incontinence and bowel disturbances) and a lowering of the quality of life that an eventual diagnosis would lead to.

2.1.2. Beneficence, non-maleficence and utilitarianism

All doctors learn the Hippocrates' oath: "Primum non nocere" (*lat.*) – first do no harm. Any potential benefits derived from screening for PC need to be weighed against any potential negative aspects and the potential harms of screening, including the diagnostic procedures, the treatments for PC and the morbidity and mortality aspects. Almost all treatments for PC have side-effects, for early stage tumors as well as for advanced disease. With PC screening, would it be ethically justifiable to cause side-effects/harms to "innocent subjects" to achieve benefits for others? However, for some men, early treatment in itself can be valuable. In a randomized Swedish study, men reported similar (or indicated even better) quality of life after 15 months to two years after radical prostatectomy compared to men assigned to watchful waiting²³⁵. Adjusted for several confounders, another study showed better mental health scores for men who had undergone radical prostatectomy as compared to radiotherapy and men on watchful waiting³⁰⁵. There are also indications that men selected to active surveillance report favorable anxiety levels compared to reference values in the literature of men undergoing other PC treatments.²⁰⁹

At present, screening offers a possibility to diagnose early PCs that can be successfully cured. At the same time, screening may also detect indolent cancers that do not form a threat to the patient's life. With screening, there is a risk of over-diagnosis and over treatment^{120,251}. A screening program ought to provide benefits and to balance them against risks. The potential benefits of PC screening on a population-level are reductions in PC-specific mortality and morbidity, but how can these benefits be interpreted on an individual level? An illustration of some examples is given in table 2:

Table 2 Examples of different outcomes of screening as well as in the absence of screening

	SCREENED				UNSCREENED		
	Man A	Man B	Man C	Man D	Man E	Man F	Man G
OUTCOMES:	Early detection, cured on time, PC mortality reduced Labeled "patient" for many years, suffers from side-effects of treatment but is saved from PC death.	Early detection, early treatment, less morbidity than the diagnosis at an advanced stage in a clinical setting; saved from needless suffering	Early detection of low risk tumor; the man feels safe and secure under an active surveillance program	"Over-diagnosed", latent PC, clinically insignificant cancer that will never cause symptoms or pose a threat to the man's life; he is unnecessarily "labeled" patient for many years and perhaps also immediately (or later on) treated unnecessarily and suffers from the side-effects of treatment.	Unaware of the diagnosis until its clinical presentation; the cancer is found too late; he suffers tremendously from the morbidity of the disease and from the treatment if that affects his quality of life. Later, he dies, either from the disease itself or from an event associated with the treatment or from inter-current death.	Unaware of the diagnosis; latent indolent cancer that will never give any symptoms or pose a threat to the man's life.	Initially unaware of the diagnosis; is not labeled cancer patient, does not suffer from side-effects from unnecessary treatment Later, the cancer surfaces clinically, the patient is treated with hormonal therapy that affects his quality of life, but dies of a heart attack or other competing mortality.
"Ethical profit"	+	+	+			+	+
"Ethical loss"	-				-	-	-

Whether the sum of all “ethical profit” and all “ethical loss” is beneficial for the group of men that undergo screening as compared to the same calculation for men who do not is not known today. Some authors, in favor of screening, claim: “It would make sense to try to minimize the psychological and medical effects of a diagnosis of low-risk PC rather than to deprive some men of an effective means of detecting and treating a high-risk cancer just because we are afraid of adversely affecting a whole lot of other men.”³⁰⁶ Other authors claim that the number of men who will not benefit from screening will exceed the number of men who will. The number needed to screen and to treat to prevent one PC death that should be regarded as acceptable is an issue for debate.

We know that screening with PSA reduces PC mortality (“man A” as compared to the situation for “man E”)³⁹ and PC morbidity (“man B”)¹⁰⁸. However, we also know that PC screening with PSA is associated with over-diagnosis (“man D”)³⁹ and that many men have asymptomatic PC without ever knowing it during their life time (“man F”)¹²⁹, as clearly shown by autopsy studies of men dying from other causes¹²⁹.

As a result of screening, many men will have to live several years as cancer patients, without experiencing the benefits of early detection because their disease will not progress to cause symptoms or death. Some have estimated the number of over-diagnosed men to be high since the introduction of the PSA test in the U.S.³⁰⁷ Receiving a cancer diagnosis is always a turning point in an individual’s life, not necessarily negatively, but often markedly. Both localized and advanced PC have an influence on men’s daily lives. However, many men find a way to live in balance in their new situation and sometimes even with positive changes in their lives.³⁰⁸

Utilitarianism

Because public health policy decision-makers are mainly population oriented, they often determine priorities with the help of the utilitarian approach. It is an ethical theory founded by Jeremy Bentham, James Mill and John Stuart Mill in England in the 19th century. The theory claims that “that action is best that produces the greatest good for the greatest number”.³⁰⁹ Bentham (1748-1832) believed that the moral rightness (or wrongness) of an action can be found by adding up the amount of pleasure or pain that it produced, the so-called “hedonic calculus”. The doctrine of utilitarianism sees maximization of utility (for example, given a benefit) and minimization of disutility (not given a benefit) as moral criteria for the organization of a society. The morally best act is thus the one that maximizes human welfare, giving equal weight to each person’s welfare, “the greatest good for the greatest number, regardless of who receives it”. The right choice is the one that produces the greatest reduction in the total burden of the disease. Utilitarianism therefore permits calculations of QALY’s (quality-adjusted life years) and DALY’s (disability-adjusted life years) as well as cost-effectiveness analyses.

The decision on PC screening could be based on a utilitarian rationale under the assumption that the main goal is to create the greatest utility for the society as a whole, with utility measured according to the health benefits directly resulting from PC screening. The morally right choice would then be the one that produces “the largest

reduction in the burden of disease”, for example in terms of more deaths averted and life-years gained with or without screening. The decision-makers might be regarded as objective utilitarians, “a group of experts which define an index that embodies the rationally knowable components of well-being”³⁰¹. Their choice would rely upon numerical indicators of health benefits, instead of personal assessments of health gains.

The goal of offering early diagnosis must be to decrease the burden of suffering and potential death from PC. If treatment is very efficacious, the cost-effectiveness of screening may be reasonable; if treatment is less efficacious, the results may be net harm and high costs¹³⁰. With limited resources, investing in early-detection services for PC requires an understanding of all the resource costs (for instance, physician’s time, laboratory tests, patient’s time away from work)³¹⁰ together with the costs associated with follow-ups, treatments, hospital care et cetera.

Cost-effectiveness analyses

De Koning et al., from the Netherland’s branch of the ERSPC provided a way to calculate preliminary estimates on the benefits and harms of PC screening based on the current evidence from ERSPC and the literature (personal communication)³¹¹. These calculations may be regarded as built upon utilitarian beliefs. The estimates can be informative in a cost-effectiveness analysis that can be combined with a quality of life (QoL) analysis. Cost-effectiveness analyses will estimate the ratio of resources used (costs) and the health benefits achieved (effects) with PSA screening compared to a situation without screening. Cost-utility analyses will consider added life years and the benefits achieved, together with QoL. The benefits of screening could be calculated from PC specific mortality reduction, life years gained and reduction in advanced disease. The harms could be calculated from estimates of over-diagnosis, over-treatment and lead time years. Utilities could be expressed in terms of values of QoL for a man who dies from PC compared to a man in full health, taking into account the QoL from different treatment options. The duration of time with loss in utility is corrected for. These types of calculations will be of the utmost importance in the nearest future.

The basis for discussing population-based PC screening in several countries throughout the world will greatly depend on the outcome of QoL- and cost-effectiveness studies.³¹¹ With utilitarian calculations, focus is on the benefits on a population level. Utility maximization is an important criterion for guiding decision-making in public health. However, utility can sometimes be difficult to measure. For instance, when treatment options are chosen for PC, a man’s age is taken into account; many elderly men are more unlikely to die from the disease and more likely to suffer from co-morbidities that can serve as contra indications to curative treatment. However, a man’s chronological age of, for instance, 80 years may correspond to a biological age of 70. Similarly, a symptom such as impotence may be regarded as less severe (though still severe to some) compared to pain, nausea and anxiety in the palliative stage of PC.⁹

2.1.3. Communitarianism

Communitarian viewpoints are found among the Greek philosophers Plato and Aristotle. Communitarianism emerged as a response to John Rawls *A theory of justice* (liberalism). It criticized the “atomic” picture of the human being as “a dimensionless dot in no context who knows what is right or wrong”. Michael Sandel (1953-) who at that time was a student of Rawls at Harvard University, counter argued that the human being becomes an individual through response to values and beliefs in a society³¹². While the view of liberalism is that all individuals should stand back and personally assess what is right, the communitarian response is that this is impossible, because the self is “encumbered” or embedded in a community.³¹³ From a relative communitarian perspective, an individual is shaped in the context that he or she lives in, and formed by the moral values that are defined by that particular community. Because the individual “selves” are encumbered in the community they are not always capable of making the best decisions. Therefore, various degrees of paternalism, responsive to the values in the community, may be advocated applying this ethical framework as opposed to the liberal view, which has little tolerance for paternalism but expects the state to be neutral. Communitarians do not prioritize individual rights and self determination, but rather define what is good based on community values, thus allowing the state to take a position on what is right and wrong. Decision-making should be based on the norms that exist in that community, and will thus consequently have contextually-dependent outcomes. In contrast to utilitarianism, communitarianism does not rely on cost-effectiveness analyses or hedonic calculations in terms of the total burden/benefit for this particular community. Assuming a relative communitarian view, whether to screen or not, would depend on what values and norms are believed to increase well-being and what is regarded as “good” in the community. Paternalism can act in both directions.

2.1.4. Conclusions from ethical considerations

In conclusion, a synthesis of the “four-principle approach” and the three philosophical views of liberalism, utilitarianism and communitarianism cannot yield a definite answer for public health policy decision-makers on PC screening, on the evidence available today, 2010, but they can perhaps provide an arsenal for a structured ethical analysis in the future. The ethical analysis can, at present, act in both directions. Utilitarian calculations are under way. A public health advisory committee, government or similar has a moral obligation to serve the public welfare by increasing overall public health, in a way that is also fair and equitable. The concept of autonomy indicates that information should be provided to men about the benefits and limitations of testing so that an informed decision about it can be made with the clinician’s assistance.

One compromise, and possibly the most ethical choice from an autonomy point-of-view, between completely voluntary screening and mandatory screening (*here: strongly recommended/encouraged*), would be to opt for mandatory information and *offering*.³¹⁴

3. AIMS OF THE THESIS

Background to the studies forming the thesis

This thesis reports on the main outcomes of the Göteborg randomized population-based prostate cancer screening trial. This study is registered as an International Standard Randomised Controlled Trial (<http://www.controlled-trials.com> number ISRCTN54449243). The thesis attempts to answer the following questions: Does PSA screening reduce PC mortality and what are the potential negative consequences for men undergoing such screening?

In 2009, a 20% disease-specific mortality reduction at 9 years of follow-up was reported for men in the core-age group in the ERSPC study³⁹. This report was important as it contributed the first “level 1 evidence” that PSA-based PC screening can reduce PC mortality. However, the simultaneously released report from the U.S. PLCO trial found no difference in PC mortality between men randomized to screening and those in the control group at 11.5 years’ follow-up.⁴⁰ In an editorial comment, Barry argued that longer follow-up was needed before any definitive conclusions could be made.³¹⁵

Whether the benefit would increase with longer follow-up is now being investigated. The Göteborg randomized population-based prostate cancer screening trial now has 14 years to report in answering this key question. The study design allows for an analysis of both how a screening program will be received by the population and also its effectiveness in terms of PC mortality reduction on a population level. It allows for the calculations of the number needed to screen and treat to prevent one PC death.

One objection to population screening in general, has been the assumption that invitation to and participation in screening examinations for cancer cause psychological distress^{316,317-318}. This thesis therefore deals with the psychological effects of the screening procedures, especially among men with elevated PSA, repeatedly examined for PC.

Due to the low specificity of PSA, PC screening will unavoidably involve a large number of prostate biopsies. Despite being an invasive and sometimes uncomfortable procedure, prostate biopsy is regarded as safe and acceptable^{254, 319} with a low rate of major complications but with frequent minor complications³²⁰. Although rarely encountered, a few cases of fatal outcome after prostate biopsy have been described in the literature^{319, 321-329}. The majority of cases have been due to septicemia; either anaerobic (bacteria) or due to *Escherichia coli* (bacteria). A few cases (mainly case-reports) of profuse potentially life-threatening rectal hemorrhage have been reported; some have required different types of interventions, but, to the best of our knowledge, there are no reported fatalities from rectal bleeding.³³⁰⁻³³⁹ Although direct causes such as sepsis and rectal hemorrhage seem to be very rare causes of deaths after prostate biopsy, these complications might increase the risk for death from other causes. Many men who are referred to prostate biopsy are elderly and often have co-morbid diseases such as cardiovascular disease. Whether the prostate biopsy may elevate their risk of death from existing co-morbidity (excess mortality) has not been well studied. As prostate biopsies are numerous in PC screening, attention must be paid to the potential hazards of this

common procedure. The aim of the second study was therefore to assess possible excess mortality and, in particular, deaths from sepsis and hemorrhage in men who undergo prostate biopsy within the ERSPC.

This thesis further explores the most common curative treatment option for early localized PC in Sweden³⁴⁰, radical prostatectomy, and its associated potential side-effects and risks. The operation was introduced in Sweden in the 1980's, but until the mid 1990's only a few hundred cases were operated on each year. Since then, the operation has become common and today radical prostatectomy is performed at almost all hospitals in Sweden (to a lesser extent at minor hospitals). In 2006, more than 2,000 radical prostatectomies were performed in Sweden.²¹⁹ In previously published papers, radical prostatectomy has been associated with very low perioperative mortality, varying from 0.1 to 0.5%, but many of these series represent high-volume centers and/or centers with a long experience of the operation³⁴¹⁻³⁴⁶. The aim of the fourth study was to assess the risk of the worst possible side-effect, i.e. mortality due to the operation, measured as the 30-day mortality rate, in a nationwide survey in Sweden.

Moreover, screening programs for PC pose a potential risk for adverse side-effects following treatment with curative intent for early detected tumors. Despite the reduction in disease-specific mortality achieved with screening, there is a need for ethical considerations to ensure that the benefits outweigh the harms if general PC screening were to be introduced on a population level. Most cancers detected in an organized screening program are early stage tumors that are suitable for treatments with curative intent. In the literature, the incidence of post-prostatectomy potency rates varies widely between 11% and 87%²³⁶⁻²³⁷ and post-prostatectomy incontinence between 0% and 87%²³⁶⁻²⁴⁰. In order to get a balanced picture of screening for PC, there is an urgent need to evaluate the potentially negative side-effects following treatment in the screening trials. The final study therefore investigated the main side-effects of radical prostatectomy, impotence and incontinence translated into population-induced risks. As the study is truly population-based with up-front randomization, it should be possible to calculate reliable estimates on how much more surgically-induced morbidity screening will cause on a population level if a screening program were to be introduced.

The studies outlined in this thesis were intended to address the following questions:

- I. Does PSA screening impact disease-specific mortality at 14 years of follow-up and what are the potential negative consequences?
- II. Is screening associated with anxiety, especially among men with an elevated PSA?
- III. Is the diagnostic procedure, prostate biopsy, associated with excess mortality?
- IV. Radical prostatectomy is the most common treatment with curative intent in a PC screening program. What is the 30-day mortality after this surgery in a nationwide setting?
- V. What would be the population-induced risk of impotence and incontinence after radical prostatectomy if PSA screening were to be introduced?

4. STUDY POPULATION

As of December 31, 1994 the Population Register documented 32,298 men born between January 1, 1930 and December 31, 1944 (ages 50-64, median 56 years) living in the city of Göteborg, Sweden (440,000 inhabitants in total). Of these, 20,000 men were randomly allocated (without prior information) in a 1:1 ratio to either a screening group invited for biennial PSA testing, or to a control group not invited. Subsequent to randomization, we excluded 56 men with a prior diagnosis of PC, 34 men who had died, and 6 men who had emigrated before the randomization date (these latter individuals were not yet removed from the Population Register at the time of randomization). The Ethical Review Committee at the University of Göteborg approved this study. The study began to invite men in January 1995, and in 1996 the study was associated to the European Randomized Study of Screening for Prostate Cancer (ERSPC), without any changes in the protocol. Figure 7 depicts the study design.

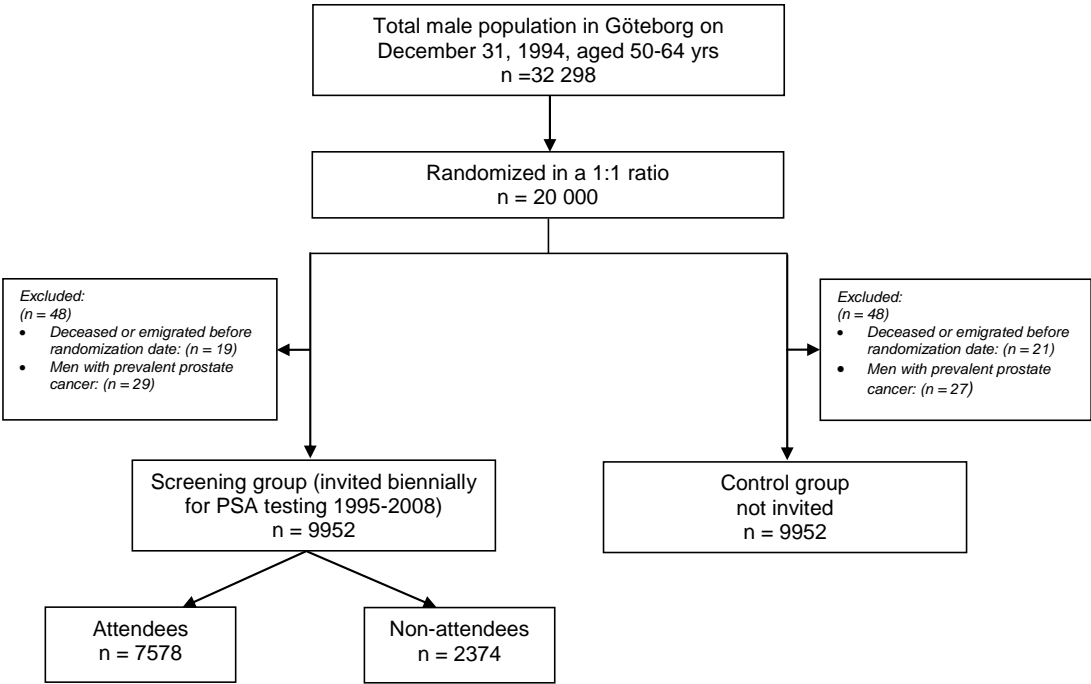


Figure 7. Consolidated Standards Of Reporting Trials (CONSORT) diagram showing the screening algorithm of the Göteborg randomized population-based prostate cancer screening study between 1995-2008. PSA indicates prostate-specific antigen.

The Göteborg randomized population-based prostate cancer screening study constitutes the basis for this thesis in all its papers except for **paper IV**.

In **paper I**, 9,952 men randomized to biennial invitation for PSA testing 1995-2008 were compared with 9,952 men randomized to no such testing (regular care) with respect to PC incidence and mortality.

In **paper II**, 1,781 men with a positive screening test (PSA >3 ng/mL) referred to further clinical investigation with prostate biopsies were studied with respect to anxiety levels.

In **paper III** we studied short-term overall (here: other cause than PC) mortality for a cohort of 12,959 first-time screening-positive men (i.e. with biopsy indication) and a cohort of 37,235 first-time screening-negative men. This is a multi-center study within the ERSPC in which Finland, The Netherlands and Sweden participated.

Paper IV, is a nationwide (Sweden) population-based study assessing 30-day mortality after radical prostatectomy. In this, all men diagnosed with localized PC (≤ 70 years, clinical stage T1-2, PSA <20 ng/ml) who underwent radical prostatectomy in Sweden between 1997 and 2002 were identified through the National Prostate Cancer Register (NPCR), $n=3,700$ men. From linkage with the Inpatient Register and the National Population Register during the same period, there were 4,457 radical prostatectomies performed (this covered all men who underwent radical prostatectomy because of PC regardless of age, PSA level or clinical stage).

After 14 years, 1,856 men were detected with PC; 1,849 when excluding seven cases, detected at autopsy in the control group. Of these, 1,047 received treatment with curative intent. Open radical prostatectomy was performed in 829 cases (562 screened, 267 controls). In **paper V**, 294 of these men participated in a sub-study (205 screened, 89 controls). These men underwent radical prostatectomy at Sahlgrenska University Hospital between 2001–2008 and were registered in a quality assurance database in which side-effects from treatment were recorded.

5. METHODS & STATISTICS

- In **paper I** and **paper V**, the analysis was made according to the intention-to-screen principle, i.e. comparing men randomized to the screening group (attendees and non-attendees) with men randomized to the control group.
- In **paper I-III**, and **paper V**, data have been prospectively collected, and longitudinally analyzed statistically in **paper II** and in **paper V**.
- **Paper III** is a prospective cohort study following men with and without a biopsy indication.
- **Paper IV** is a registry linkage study.

Paper I

Methods

The aim of **paper I** was to evaluate the effects of PSA screening on PC incidence and PC mortality after 14 years. Men allocated to the screening arm were invited every second year for PSA testing, until they reached the upper age limit of 70 years (mean 69 years, range 67-71).³⁴⁷ Men with PSA below the threshold were not further evaluated, but were invited again after two years. Only men with PSA at or above the threshold were invited for further urological work-up including digital rectal examination, trans-rectal ultrasound examination, and at least laterally directed sextant biopsies. For men diagnosed with PC, the protocol did not specify any particular treatment; further evaluation and treatment was at the discretion of their physicians. Men with a benign biopsy were re-invited for screening after two years. Men with persistently elevated PSA were recommended a new prostate biopsy at each visit PSA was elevated. Seven screening rounds were completed by the end of 2008. Minor changes in the PSA-cut-off and in the screening algorithm were made during the study period.³⁴⁸

In both arms of the study, the incidence of PC was checked by linking with the West-Swedish Regional Cancer Registry every third month since the study started. For every man with PC, all available medical documentation was retrieved for establishing tumor stage, treatment, and disease course. In addition, for all deceased men we obtained a copy of the cause of death (COD) certificate. Causes of death for men diagnosed with PC were determined by an independent COD committee. The committee performed a blinded review of all cases diagnosed with PC (including all medical records, pathology reports, autopsy protocols) according to a standard algorithm used in the ERSPC.³⁴⁹ The COD certificates were not available to the COD committee. Deaths classified as definitive PC deaths, intervention-related deaths (i.e. deaths from diagnostic procedures or treatment), or probable PC deaths were regarded as being caused by PC, while other classifications were regarded as non-PC deaths.

Statistics

The main outcome measures were absolute and relative risk reduction in cumulative PC mortality between study arms. Secondary measures were the cumulative PC incidence and the proportion of screening attendees. A pre-study power calculation (two-sided test, $p < 0.05$ and 80% power) was performed on the assumption of a 70% participation rate. A 40% mortality difference between the study arms was calculated to become significant 15 years after the study start (at the end of 2009). A new power calculation in 2009 incorporated the observed 76% participation rate in the Swedish branch in the published ERSPC results.³⁹ The new calculation implied significant power to analyze the data through 2008.

Cumulative incidences of PC in screening and control groups were plotted as 1 – the Kaplan-Meier estimator. The corresponding hazard ratio for the incidence of PC between the groups was estimated by Cox regression. The proportional hazard assumption was tested with Schoenfeld residuals³⁵⁰. A time-dependent covariate approach was used to estimate the hazard ratio at different time periods after the start of screening to avoid violence to the proportional hazard assumption. The Nelson-Aalen method was used to calculate the cumulative hazard for PC mortality.³⁵¹ Poisson regression analysis was used to estimate the rate ratio of mortality in the screening group to the mortality in the control group. All p-values were two-sided. The number needed to screen (NNS) was calculated as $(1/\text{absolute reduction in PC mortality})$. As this study is an intention-to-screen analysis, we refer to NNS as number needed to invite for screening. The number needed to treat (NNT) was calculated as $((1/\text{absolute reduction in PC mortality}) * \text{excess PC incidence})$. This measure was also rephrased to number needed to diagnose, because many patients actually were not treated.

Paper II

Methods

The aim of **paper II** was to evaluate the degree of anxiety among men who turned out to be screen-positive, i.e. those who had elevated PSA values (>3 ng/mL) within the screening trial. Men with a positive screening test (elevated PSA) referred to biopsy were requested in the waiting-room to answer a study-specific self-administered questionnaire on anxiety awaiting the PSA test result and anxiety associated with the invitation to further clinical work-up (including prostate biopsies). A secondary objective was to study the possible influences of age, PSA level, heredity, lower urinary tract symptoms, biopsy finding and round of examination on levels of anxiety. Men with elevated PSA were informed of their PSA result through a standardized letter. In the same letter these men were invited to a clinical examination and they were informed that they had about a 15% risk of PC. Men with elevated PSA and benign biopsy findings were re-invited for biennial measurement of PSA. In this study, five screening rounds were completed and analyzed (1995-2005).

Statistics

Descriptive statistics were calculated using conventional methods. A multinomial logistics model for repeated measurements of individuals was performed to analyze the impact of the covariates age, PSA level, heredity, symptoms of urinary outflow obstruction, irritative urinary symptoms, biopsy finding and round of examination on anxiety. To avoid selection bias, only men with repeated measures (longitudinal data) were incorporated into the multinomial logistics model. We assumed that the data followed a proportional odds model when analyzing the impact of these covariates (which were dichotomized). The intensity of lower urinary tract symptoms was analyzed statistically as 'No symptoms' or 'Symptoms' (including minor or major symptoms). Odds ratios (ORs) and confidence intervals (CIs, 95%) for all covariates were calculated. The relative risk (RR) was calculated using conventional methods when analyzing the probability of reporting high levels of anxiety at repeated screening. The Chi-square-test was used for testing the level of significance. The possible relationship between non-participation rate and degree of self-reported anxiety was also analyzed by means of the Chi-square-test. P values <0.05 were considered significant.

Paper III

Methods

The ERSPC was initiated in the early 1990's³⁵². Screening protocols, practices and referral criteria for further examination with prostate biopsies differ between the centers within the ERSPC. Biopsy indication for the absolute majority of screens was based on a PSA level of ≥ 3 or initially 4 ng/mL in some centers, but some additional criteria were also initially included such as digital rectal examination findings, trans-rectal ultrasound findings and the ratio of free to total PSA (for definition per center, see website)¹⁰³. Strategies of antibiotic treatment, use of local anesthetic agents as well as pre-biopsy regimens with respect to rectal cleansing enemas differ somewhat. All three centers in the present study (Finland, The Netherlands and Sweden) prescribe screen-positive men laterally directed, sextant (at least), trans-rectal biopsies of the prostate. In most cases, men with a biopsy indication underwent clinical examination by an experienced urologist, including medical history, digital rectal examination (DRE) and trans-rectal ultrasound. The study protocols prescribe all men with a biopsy indication to undergo biopsies, but the urologist responsible has the final decision to refrain from biopsy in cases with (severe) co-morbidities.

In the present study, 50,194 screened men with at least one eligible screen were identified and were prospectively followed with overall mortality (other cause than PC mortality) as major outcome. A positive screen was defined as an eligible screen resulting in biopsy indication and was found in 12,959 men, while 37,235 men had only negative screening tests. The median PSA for screening-positive men was 4.5 ng/mL (quartiles Q1 3.5; Q3 6.0) and for screening-negative men 0.9 ng/mL (Q1 0.6; Q3 1.4). The age at screening ranged between 50.2 and 78.4 years. The mean age at screening was 64.8 (SD 5.0) years in the screening-positive group and 61.2 (SD 5.2) years in the screening-

negative group. Of the group of screening-positive men, 11,721 (90.4%) actually underwent biopsy (mean age 64.7 years, SD 5.0) and 1,238 (9.6%) did, for various reasons, not undergo a biopsy (mean age 65.8 years, SD 5.2). Of the latter, 73.8% were non-responders to the clinical examination and 26.2% underwent examination but were not biopsied. Of those with a positive screening test, 59.4% underwent biopsy within the first month after screening and 94.0% within 3 months.

Statistics

Mortality rates were calculated within 30, 60, 90, 120 and 365 days after the screening test and was compared between the two groups. Cumulative mortality at 120-days and one year was calculated by the Kaplan-Meier method, with statistical significance evaluated using the log-rank test. Incidence rate ratios and statistical significance were evaluated using Poisson regression analyses (taking the follow-up time into account), adjusting for age and total-PSA level (continuous variables), screening centre and whether a biopsy indication was present, or whether a biopsy was actually performed or not, respectively. A p-value < 0.05 was considered statistically significant. Furthermore, the cause of death was collected in screening-positive men who had undergone biopsy and who died within 120 days of the screening test. Men who died from PC within the study period (1 year) were censored at the time of PC death (n = 6).

Paper IV

Methods

The incidence of PC in Sweden is increasing rapidly, as is treatment with curative intent. Radical prostatectomy is currently commonly performed, either within or outside large high-volume centers. The aim of the study for **paper IV** was therefore to assess the 30-day mortality rate after radical prostatectomy in Sweden. In this nationwide population-based study, all men diagnosed with localized PC (< 70 years, clinical stage T1-2, prostate-specific antigen < 20 ng/ml) who underwent radical prostatectomy in Sweden between 1997-2002 were identified through the National Prostate Cancer Register (NPCR). Mortality within 30 days was analyzed through linkage between the follow-up study of the NPCR and the Regional Population Registers. The cause of death in death certificates was compared with data from the hospitals. A letter with a questionnaire on the cause of death and co-morbidity was sent to the hospital concerned regarding any possible relation to the operation, and at the same time assessing patient co-morbidity. The death certificates for these men were requested and were compared with the questionnaires retrieved from the hospitals. To validate the results, a record linkage between the Inpatient Register and the National Population Register was also performed. The total number of radical prostatectomies per hospital during the period was calculated and the definition of high-volume hospitals by Begg et al. was used (an annual average of at least 28 operations)³⁵³.

Paper V

Methods

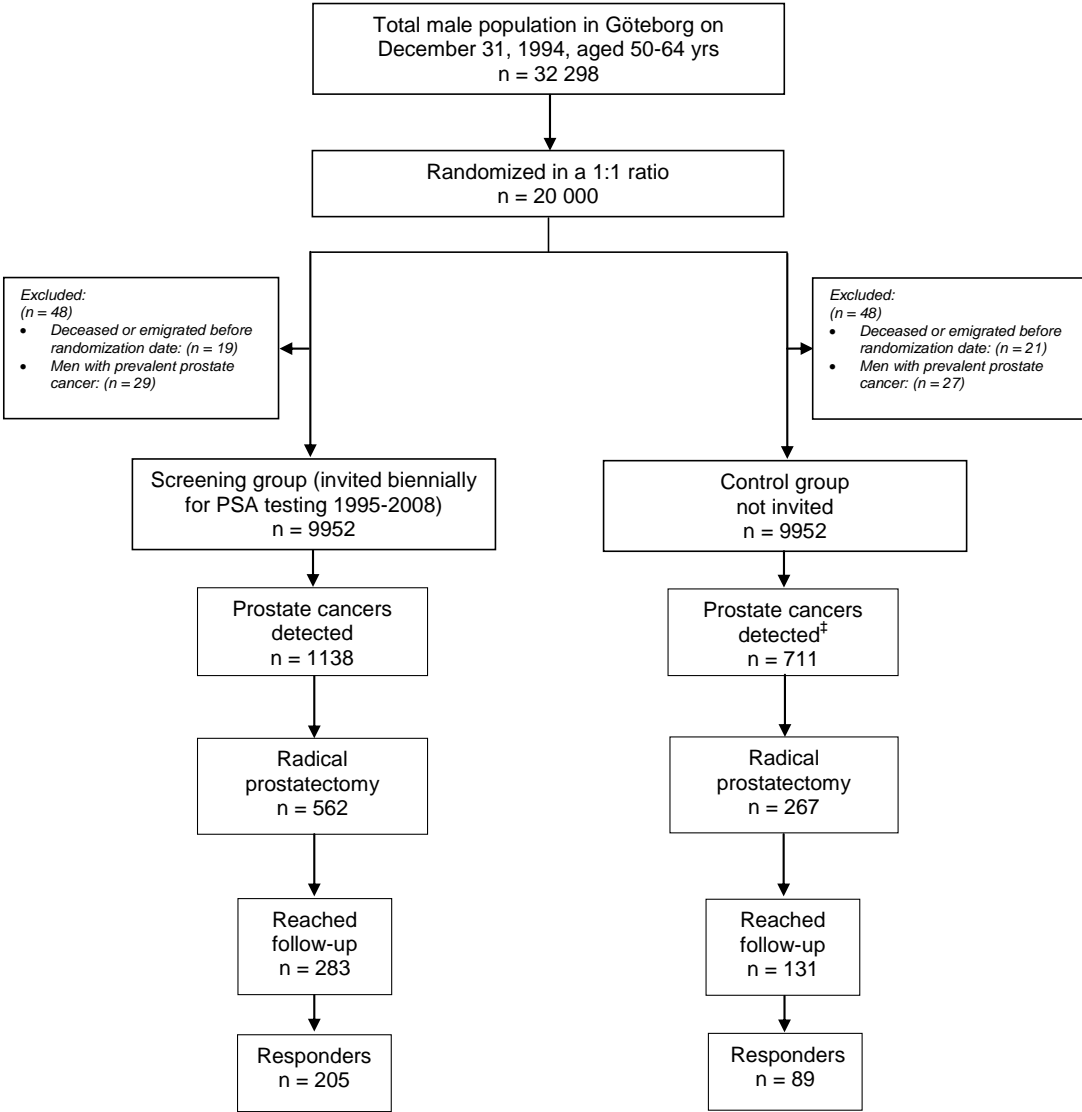
In **paper V**, the frequencies of side-effects in a subset of men detected between 1995-2008 and treated with radical prostatectomy between 2001-2008 in the Göteborg randomized population-based prostate cancer screening trial were extrapolated to the whole study.

Beginning in January 1, 2001 all men operated upon with radical prostatectomy at the Sahlgrenska University Hospital were entered into a quality assurance database including pre-operative and 18-month postoperative evaluation of erectile and urinary function. Men belonging to the screening study (screened men and controls) and operated upon between 2001 and 2008 formed the study population. Erectile function was assessed using the validated and internationally well-established International Index of Erectile Function (IIEF)-5 questionnaire as described by Rosen et al.³⁵⁴ Men who reported use of alprostadil were incorporated into the impotency group, regardless of which IIEF-5-score they reported with this use, whereas use of PDE-5 inhibitors was not taken into account. Hospital records were reviewed for all men who underwent surgery after 2001 and who were sent questionnaires preoperatively and at 18 months, but for whom one or both questionnaires were missing (non-responders). A questionnaire regarding urinary incontinence was also included. The answers were measured on a five point scale ranging from 0-4, where a score ≥ 2 was supportive of urinary incontinence. This questionnaire has previously been used when measuring postoperative urinary continence after robot-assisted laparoscopic radical prostatectomy³⁵⁵.

Statistics

Analyses were made according to intention to screen and compared screened men with controls (i.e. standard clinical care). Data was extrapolated from our results (patients operated upon from 2001-2008) to the full screening setting with 14 years of follow-up. Extrapolated numbers of pre-operatively partially or fully potent and sexually active men were derived from the proportion of men with an IIEF-5-score of 12-25 and of these, the numbers of post-operatively impotent or sexually active men were derived from the proportion of impotent men or men who reported no sexual activity at 18 months. Extrapolated numbers of post-operatively incontinent men, among all the men who underwent surgery, were derived from the proportions of men reporting urinary incontinence grade 2-4 at 18 months of follow-up.

Figure 9 depicts the study design.



(‡ excluding 7 cases detected at autopsy)

Figure 9. Study design

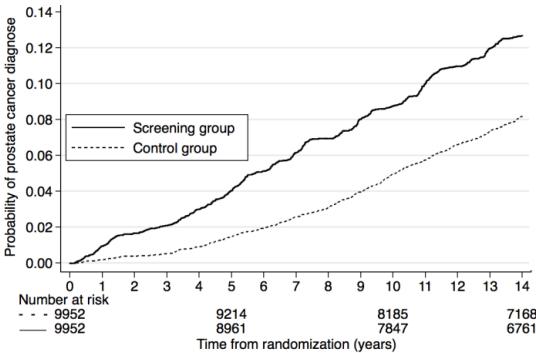
6. RESULTS AND COMMENTS

Paper I

This paper reported the first planned report on cumulative PC incidence and mortality calculated up to December 31, 2008, i.e. a median follow-up of 14 years. Screening and control groups each consisted of 9,952 evaluable men. In the screening group, 76% participated in at least one screening round (attendees). In 2,469 men (33%), PSA was elevated above the threshold at least once. Among these men with elevated PSA, 2,298 men (93%) underwent prostate biopsy at least once.

PC was diagnosed in 1,138 men in the screening group and 718 in the control group. The cumulative incidence of PC at 14 years was 12.7% in the screening group versus 8.2% in the control group, corresponding to a hazard ratio of 1.64 (95% confidence interval [CI] 1.50-1.80, $p < 0.0001$). (Figure 10)

Figure 10. Cumulative incidence of prostate cancer in the study



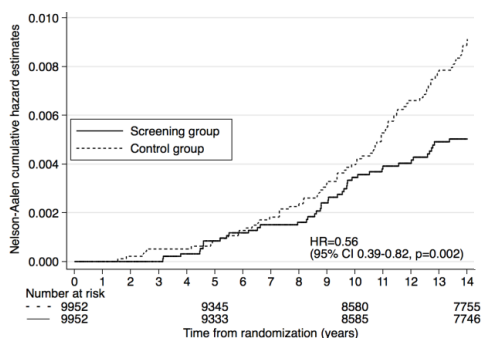
The majority of PCs diagnosed in the screening group were early-stage disease. The number of men with advanced PC (metastases or PSA >100 ng/ml at diagnosis) was lower in the screening arm: 46 men compared to 87 in the control arm ($p = 0.0003$). Among the non-attendees in the screening group, a higher proportion of cancer cases were advanced at diagnosis than among attendees.

The difference in stage distribution was mirrored by treatments, with more hormonal therapy in the control arm and more surveillance, or treatment with curative intent in the screening arm. However, among men with low and moderate-risk tumors, the proportion receiving curative treatment was similar between trial arms: 476/967 (49%) in the screening arm and 228/448 (51%) in the control arm. Among the men diagnosed with PC, the median follow-up after diagnosis was 6.7 years in the screening group and 4.3 years in the control group. In evaluating whether deaths were attributable to PC, the COD committee and COD certificates were highly concordant. According to the COD committee review, 78 men in the control group died from PC (77 according to death certificates) compared to 44 (45 according to death certificates) in the screening group. Within the screening group, 27 prostate-cancer-specific deaths were registered among 7,578 attendees versus 17 among 2,374 non-attendees. Among attendees who died from

PC, 13 were diagnosed with PC at their first screening visit (prevalence screen), and the youngest of these men was 59 years at diagnosis. Of men born 1930-34, i.e. older than 60 years at study entry, the number of PC deaths was 19 among attendees versus 35 among controls. These attendees seemed to be at higher risk of PC death relative to attendees of younger age at the study start. Of the younger men born 1935-44, only 8 PC deaths occurred among attendees as compared to 43 among controls.

The main outcome analysis performed on intention-to-screen showed that the RR of dying from PC was 0.56 (95% confidence interval, CI, 0.39-0.82, $p=0.002$) in the screening compared to the control group. The absolute cumulative risk reduction (Kaplan-Meier estimates) of death from PC at 14 years was 0.40% (95% CI 0.17-0.64%), from 0.90% in the control group to 0.50% in the screening group (Figure 11). The RR of dying from PC among attendees compared to the control group was 0.44 (95% CI 0.28-0.68, $p=0.0002$) and the RR between non-attendees and the control group was 1.05 (CI 0.62-1.78 $p=0.84$).

Figure 11. Cumulative prostate cancer mortality in the study



The number of men needed to invite for screening (NNS) to prevent one PC death was calculated as 293, while the number needed to diagnose (NNT) was calculated as 12. If the calculations were restricted to attendees, the respective numbers were 234 and 15. These figures compare favorably with breast cancer and colorectal cancer screening.

The conclusions of **paper I** is thus that PSA screening is well accepted by the general population and may result in a relevant reduction (by half) in cancer mortality greater than what has been seen in screening for breast or colorectal cancer. A disadvantage of PSA screening is the long and varying lead time, resulting in a risk of over-diagnosis that is substantial although still of largely unknown magnitude.

Paper II

This paper focused on the aspects of men's reported anxiety related to the screening procedures. The aim of the study was to evaluate the degree of anxiety only among men who turned out to be screen-positive, i.e. those who had elevated PSA values (>3 ng/mL). The study specifically focused on anxiety associated with waiting for the results of PSA measurement and anxiety concerning the invitation to attend clinical examination (including prostate biopsies). Another aim was to study the possible influences of age, PSA level, heredity, lower urinary tract symptoms, biopsy finding and

round of examination. Participation rates were high (> 90%). The number of men with PSA elevation who also accepted clinical examination was high.

Levels of anxiety were assessed through self-reported questionnaires completed by 1,781 screen-positive men. During the first visit (clinical examination, including biopsies), no anxiety whilst awaiting the PSA test results was reported by 66% and 2% reported high levels of anxiety (Figure 12). Anxiety while awaiting the PSA was only influenced (increased) by the existence of previously elevated PSA tests ($p < 0.0001$).

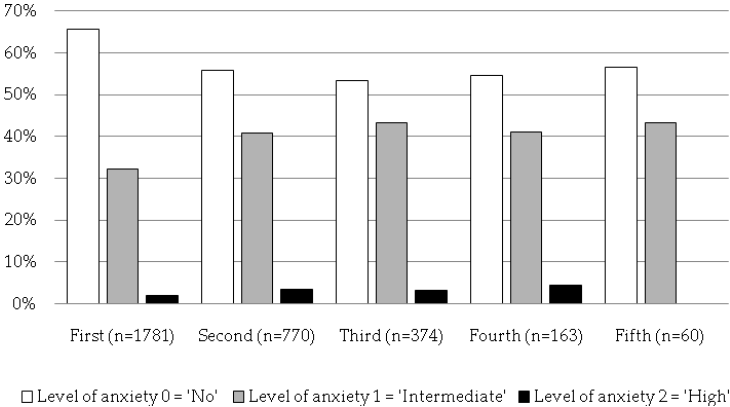


Figure 12. Anxiety awaiting the results of PSA measurement related to the number of examinations. Results are given as a percentage for every round of examination. *** $p < 0.0001$

No anxiety associated with biopsy was reported by 45%, while 6% experienced high levels of anxiety (Figure 13). Levels of anxiety decreased significantly with subsequent rounds of examinations ($p < 0.0001$) and with increasing age ($p = 0.0016$). The level of anxiety reported at first examination had a significant influence on the level of anxiety reported at subsequent examinations.

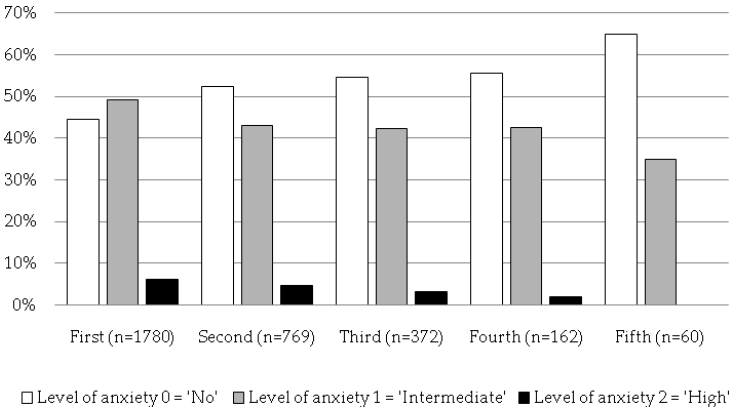


Figure 13. Anxiety associated with further clinical examination related to the number of examinations. Results are given as a percentage for every round of examination. *** $p < 0.0001$

From these results, we have reason to believe that the randomized sample of men in this study is most likely to resemble those who would participate if PC screening were to be introduced into routine practice. Considering a general, population-based screening for PC, this study indicates that the majority of men would be likely to accept an invitation. Attending a screening program for PC is seldom associated with severe negative psychological distress, even for men with persistently elevated PSA levels.

Paper III

This paper explored the risk of possible excess mortality associated with prostate biopsy in men undergoing PSA screening in the ERSPC. A group of screening-positive men was compared with a group of screening-negative men. The results show that there was no statistically significant difference in 120-day mortality between the two groups: 0.24% (95% CI 0.17 – 0.34) for screening-positive men versus 0.24% (95% CI 0.20 – 0.30) for screening-negative men, $p=0.96$ (figure 14). This implied no excess mortality for screening-positive men. As seen in figure 15, the cumulative 120-day mortality (%) was highest for screening-positive men who were not biopsied, in comparison with men who were biopsied and screening-negative men. These screen-positive men who were not biopsied had a more than four-fold risk of other cause of death during the first 120 days whereas men who were biopsied had half the risk.

Figure 14. Cumulative 120-day mortality (%) for screening-positive men (i.e. with biopsy indication) and screening-negative men (no biopsy indication)

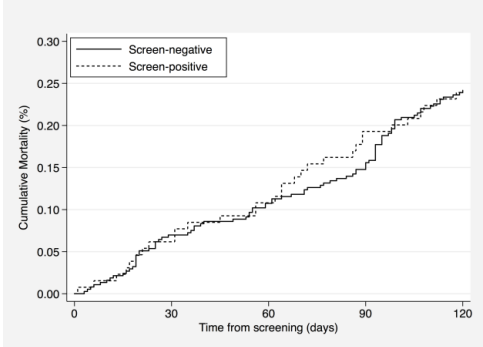
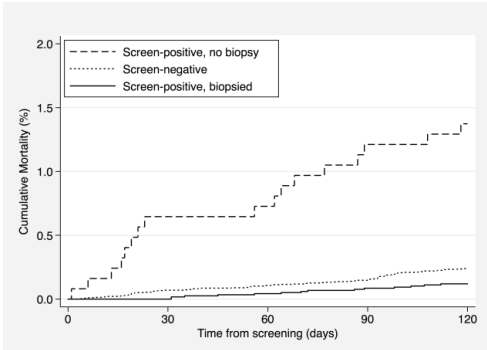


Figure 15. Cumulative 120-day mortality (%) for screening-positive men (i.e. with biopsy indication) with and without biopsy as well as for screening-negative men (no biopsy indication)



Our findings suggest firstly, a “healthy screenee effect” among screen-positive men who attend clinical examination and secondly, a “healthy selection” of those who actually undergo biopsies while attending clinical examination. Of those screening-positive who died within 120-days, 14/31 (45.2%) were in fact biopsied and in none of these cases, was death an obvious complication to the biopsy. **Paper III** is the largest study, in a screening-setting, that has evaluated biopsy-specific mortality rates as well as excess mortality after prostate biopsy in almost 12,000 biopsied men. Our findings confirm that biopsy-related death is infrequent and thus not a valid reason per se not to consider population-based PC screening programs.

Paper IV

This paper is a registry-linkage study that assessed the 30-day mortality rate after radical prostatectomy in Sweden. The results show that the number of radical prostatectomies performed increased over time, both for open and laparoscopic surgery (Figure 16). Among 3,700 radical prostatectomies performed, four deaths occurred during the first 30 days, yielding a 0.11% 30-day mortality rate. From the linkage with the Inpatient Register and the National Population Register during the same period, the corresponding figure was that six men were registered as dead within 30 days after radical prostatectomy of 4,457 performed yielding a 30-day mortality rate of 0.13%.

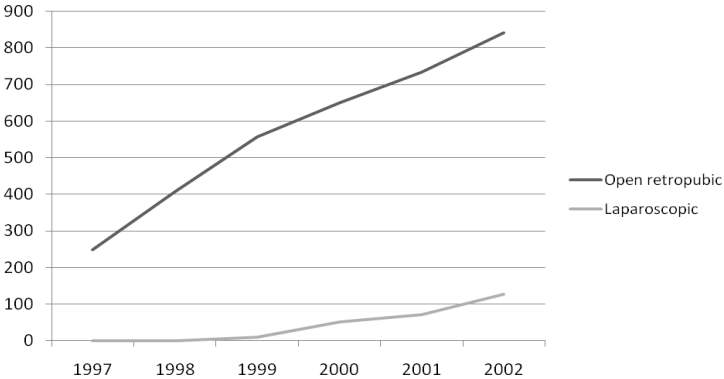


Figure 16. Number of radical prostatectomies performed in Sweden between 1997 – 2002

The four deaths in the follow-up study of the NPCR occurred at three different types of hospital (community, county and university hospital) and were all somehow most probably related to the radical prostatectomy. No evidence was found for a higher mortality in smaller hospitals; however, the few events in this study did not permit any comparison between different categories of hospitals.

Paper IV thus provides further evidence that radical prostatectomy is a procedure with very low perioperative mortality even when performed outside high-volume centers.

Paper V

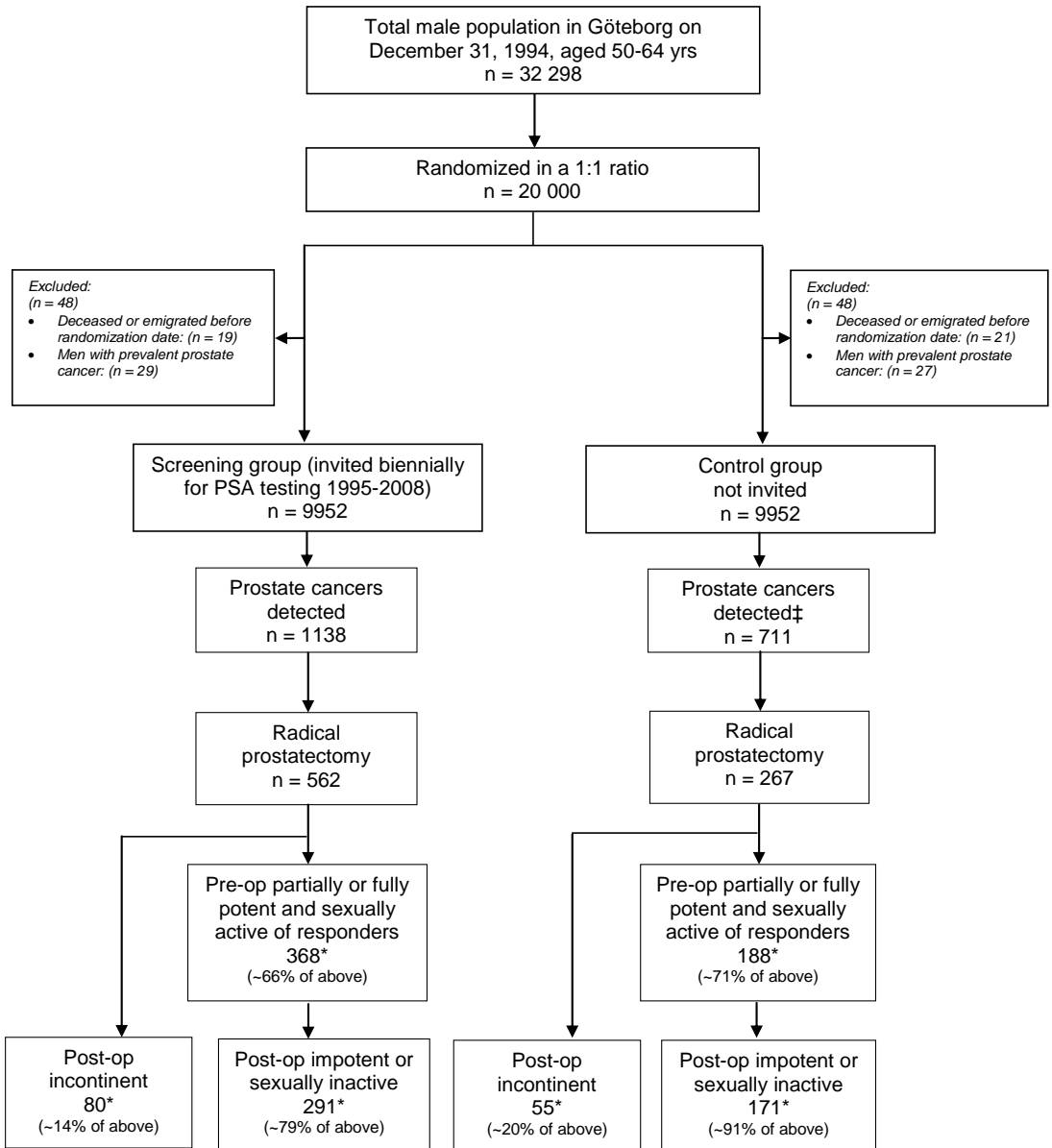
This study aimed at assessing the excess burden of side-effects from PSA screening, and more explicitly to focus on incontinence and impotence induced by radical prostatectomy. We compared men with screen-detected PC and men with PC in the control group. In both groups, men were operated upon and men unavoidably suffered from side-effects. **Paper V** aimed at quantifying how many more side-effects screening induced in the population.

Of preoperatively potent men (and of those with mild ED), 79.1% of screened and 90.7% of controls reported either no sexual activity, or an ED score ≤ 11 at 18 months after surgery. Applying the patient selection as used by Parsons et al.³⁵⁶ (age ≤ 60 years, preoperative IIEF-5-score ≥ 21 and who had a bilateral nerve-sparing procedure) yielded only 10/294 (3.4%) patients of our study population. In this small subgroup, 7/10 (70.0%) were potent (IIEF-5-score ≥ 16) at 18 months according to the criteria suggested by Parsons et al.

As regards urinary incontinence, at 18 months, 24 men (14.3%) in the screening group and 18 men (20.5%) in the control group reported some degree of incontinence (any use of pads).

Extrapolating these data in the full screening setting yielded that, with 14 years of organized PSA screening, the frequency of post-prostatectomy impotence and sexual inactivity is increased by 120/10,000 men for men subjected to screening as compared to the control population (representing the current clinical practice in Sweden). The corresponding figure for post-prostatectomy urinary incontinence (defined as use of any pad) is an increase of 25/10,000 screened men. (Figure 17)

The results of **paper I** showed a 44% relative PC mortality reduction in favor of screening, which corresponded to an absolute number of 34 PC deaths averted/10,000 screened men. In the light of **paper I**, we can now interpret **paper V** as implying that for each PC death averted with screening (34/10,000), the surgically-induced morbidity due to screen-detected PC will render four (120/34) men impotent or sexually inactive and less than one (25/34) man incontinent.



* Indicates extrapolated numbers

(‡ excluding 7 cases detected at autopsy)

Figure 17. Flow chart, 14 years of screening

7. DISCUSSION

Discussion

Paper I

The first paper in this thesis reports the longest follow-up and the largest benefit seen, this far, from a prospective, population-based randomized PC screening trial. With randomization before consent and a 76% participation rate, this program decreased PC mortality by 44% and by 56% for screening attendees, over 14 years' follow-up. Furthermore, screening induced a stage migration that reduced the risk of metastatic disease and the need for hormonal treatment.

If our screening program is regarded as successful, we suggest that the favorable characteristics of this program suggest a starting point of 50 years, a PSA threshold of 3 ng/ml or less, a not too extended screening interval and a protocol for follow-up of positive screening results with a high biopsy rate. A long follow-up time seems to be one of the most important factors for evaluating the effectiveness of screening.

The disadvantage of the program is an increased risk (RR 1.6) of low and moderate risk PC diagnosis in the screening arm. At 14 years of follow-up, the number who need to be invited to screening (corresponding to NNS) to prevent one PC death was 293, and the number who needed to be diagnosed (corresponding to NNT) was 12. These figures, and the RR of 0.56, can be compared with those of the commonly recommended practices of screening for breast and colon cancer. For mammography, a 2009 meta-analysis of randomized trials yielded a number needed to invite to screening of 377 (credible interval 230–1,050) for women aged 60-69 and 1,339 (credible interval 322–7,455) for women aged 50-59, and RR's of 0.68 and 0.86 respectively, at 11-20 years of follow-up.²⁷⁵ Separate or other mammography studies have yielded similar numbers.^{269, 280-287} In a separate 2009 Cochrane review, the NNT for mammography was 10 throughout 10 years.²⁶⁹ For colorectal cancer screening by fecal occult blood test, the RR's have varied between 0.67 and 0.87 among four randomized trials²⁸⁹⁻²⁹² and was 16% overall in both a 2008 Cochrane review²⁹³ (after 11.7–18.4 years) and a meta-analysis by Towler et al. (after 7.8–13 years).²⁹⁴ In the latter, the NNS after 10 years was estimated as 1,173 (95% CI 741–2807). A recent multicentre study presents a RR of 0.69 for colorectal-cancer mortality with flexible sigmoidoscopy screening for colorectal cancer and a lower NNS of 489 at a median follow-up of 11.2 years³⁵⁷. As screening for colorectal cancer is associated with a reduced colorectal cancer incidence, NNT is not possible to calculate for comparison.

The NNT in our study is substantially lower compared to the ERSPC publication from 2009³⁹. The NNT is very much dependent on the length of follow-up and it is not easy to predict when and at which level NNT will stabilize. Furthermore, as NNT in PC screening mainly reflects the risk of over-diagnosis it is not easy at this point to make estimates of this risk but it is probably not so high as some have feared³⁵⁸, at least if screening is restricted to the age groups included in this study. NNT in PC screening would be better rephrased as “number needed to diagnose” as many men were not

treated. As many as 314 (30%) of screen attendees were on surveillance at last follow-up in this study. This strategy will at least lower the risk of over-treatment and the risk associated seems low³⁵⁹.

Screening with PSA leads to the diagnosis of PC at an earlier stage as compared to the clinical situation ('stage migration').^{106,360} This was shown in the ERSPC trial, which revealed that 72.2% of screened men with PC had a Gleason score 6 or less.³⁹ In most cases, screen-detected PCs are organ-confined without extra capsular spread and are therefore completely curable.^{108,252} PSA screening is thought to advance PC diagnosis by 5 to 13 years.^{360,120}

Most of the PCs diagnosed in the screening group of our trial were early stage disease. This was also mirrored in the treatment differences. There was a great difference between the arms in the number of men needing endocrine treatment – 182 (1.8%) in the control group versus 103 (1.0%) in the screening group, which may be regarded as an important advantage of screening.

Although the RR of 0.56 after 14 years is considerable, the absolute risk reduction is somewhat modest (0.40%), which reflects the young age at study start and the shorter follow-up of men after PC diagnosis (6.7 years in the screening group *vs.* 4.3 years in the control group). As it takes a long time to achieve the benefit of PC screening, with only marginal benefit during the first 10 years from starting PC screening, one should be cautious to recommend screening all elderly men. As the risk of over-diagnosis and over-treatment are still the major concerns it seems questionable to invite all men over the age of 70 for PSA screening. The oldest men in our study were born in 1930, hence 64 years old at study entry in 1995. They were invited for two rounds before they terminated screening because of age. Whether continued screening for these men would have been beneficial or disadvantageous is not known.

In an earlier study, Grenabo Bergdahl et al. have shown that the majority of those men who were classified as attendees to screening and died of PC either had their disease detected at the time of the first screening round (prevalent cases), or were noncompliant with the screening algorithm/biopsy recommendations. Of 10,000 men randomized to screening, after 13 years, 18 men had died from PC, of which 12 tumors were detected in the first screening round (prevalent cases).³⁴⁷

Much of the criticism of the ERSPC can be applied also to the Göteborg trial. There could be criticism as to whether PC-specific mortality not should be the correct endpoint, but overall mortality is more relevant. However, one should not confuse a randomized screening trial with a randomized controlled treatment trial, in the latter of which overall mortality is indeed the relevant endpoint. As PC constitutes "only" a modest proportion of the total mortality for Swedish men, even a big difference in PC mortality (HR 0.56 in the present study) will only have a small impact on overall mortality (the number of overall deaths after 14 years was 1,981 men in the screening group and 1,982 men in the control group in our study). In the ERSPC trial, there was no difference in overall survival (RR 0.99; 95% CI 0.97 – 1.02, $p=0.50$). However the risk reduction seen in the present study is still clinically relevant.

How do we know that the mortality benefit was not due to more aggressive treatment in the screened group instead of the screening *per se*? Questions have been raised as to whether the mortality result seen in the ERSPC was confounded by treatment differences, i.e. that men in the screening arm were treated with curative intent at university hospitals whereas men in the control arm received other treatments or curative treatment with poorer outcomes outside the big cities. A public media debate arose when **paper I** was published online in *Lancet Oncology* on June 30, 2010³⁶¹. In a blog on the American Cancer Society's official webpage (<http://acspressroom.wordpress.com/2010/07/01/digging-deeper-into-prostate-screening-study/>) the society's chief medical officer Dr. Otis W. Brawley said: "It is important to recognize that this was not only a trial of screening alone; it was a trial of screening and superior treatment. Men in the screening group received treatment at a few centers that specialized in treatment of PC. The men in the control group received standard care in their community. That is likely to account for some and possibly all of the survival benefit."

However, this statement is not true, as this was certainly not the case in our study. All men randomized were at least at time of randomization living in the city of Göteborg and almost all patients operated on or radiated were treated at the Sahlgrenska University Hospital, so there was no difference between the groups in this respect.

There has also been a fear that patients belonging to the screening group would be treated more aggressively. From **paper I**, it may appear to some that there was a higher rate of radical prostatectomy in the screening group that could have had an impact on the cancer-specific survival outcome. More men were, indeed, treated with radical prostatectomy in the screening group in absolute numbers. As screening aims to detect cancer earlier we had more cases with early PC in the screening group compared to the control group. The fact that screening resulted in a lower PC rate was because men were diagnosed early enough to be cured by treatment. However, in **paper I**, there is no data supporting the theory fully. Rather, the treatments seemed to be very equally distributed between the two arms. In men with low and moderate-risk tumors, the proportion receiving curative treatment was similar between groups: 476 (49.2%) of 967 in the screening group and 228 (50.8%) of 448 in the control group, implying that the mortality difference resulted from screening and not from different treatments. To put it quite clearly, the rate of curative treatment was not higher in the screening group in those men in which curative treatment is an option, mainly the low and moderate risk groups. Therefore, one cannot include all the men with advanced and metastasized disease in the calculation of the rate of curative treatment as most of these men are never candidates for curative treatment. The important issue when evaluating the effect of screening is that men in the screening and control group receive the same types of treatments group by group. However, one can indeed say that **paper I** is to some extent a study of "superior treatment" or that "early invasive treatment for PC works", but that is because screening detects more tumors at a curable stage.

In the supplementary appendix to the ERSPC trial³⁹, the "overall" proportion receiving curative treatment was higher in the screening arm. However, these results

were not adjusted to stage and grade, but a “crude overall” measure. Since screening introduced both a stage and grade shift, it is not surprising that these differences were seen. The difference in treatments was in concordance with the stage distribution. In a separate analysis, the study arm had statistically significant associations with treatment with reference to the fact that especially high-risk men were more likely to receive hormonal therapy, radiotherapy or watchful waiting, but the study arm was far less important than other factors such as age, PSA level, T-stage or Gleason score. In low and intermediate-risk PC, no significantly predictive value was observed for the study arm. Therefore, no systematic discrepancy in treatment selection between arms could be shown and a mortality reduction solely caused by a treatment effect is very unlikely.³⁶²

Discussion

Paper II

Studies of adverse psychological effects from attending different screening modalities for PC have shown disparate outcomes. As many as 64% of men experiencing anxiety before prostate biopsy have been reported³⁶³ and as many as 49% of men with a benign prostate biopsy have been reported as having thought about PC either “a lot” or “some of the time”.³¹⁸ However, in a review on the psychosocial implications of PC screening, Hewitson et al. concluded that PC screening can be associated with some anxiety-raising reactions, although not sufficient to cause any deleterious effects in men.³⁶⁴

Paper II focused on anxiety related to men with an elevated PSA >3 ng/mL and anxiety related to the invitation to attend further clinical work-up including TRUS-guided prostate biopsies. Among a total of 1,781 screen-positive men included in our study, few men reported high levels of anxiety while awaiting the results of PSA measurement. Furthermore, very few men experienced high levels of anxiety regarding the invitation to attend clinical examination, despite elevated PSA levels.

These findings concur entirely with Brindle et al. who found that the receipt of an abnormal PSA test and attendance for further clinical investigation did not appear to have an impact on psychological health among men screened for PC within the ProtecT study (Prostate testing for cancer and Treatment) in the U.K.³⁶⁵ Recently, Macefield et al., working also for the ProtecT group, added further strength to our findings in **paper II** in a study using the validated Hospital Anxiety and Depression Scale (HADS) questionnaire. In the article, the authors write (under *Discussion*, p.4): “The limited published research on anxiety levels of those at higher risk by age and family history generally examined anxiety levels at PSA test, whereas here we focus on these risk groups at a further stage in the testing process. The results of this analysis build upon findings of the Swedish cohort of the European randomised study of screening for prostate cancer (ERSPC)...”³⁶⁶

In their prospective cohort of 4,198 men aged 50-69 with a PSA >3 ng/mL, age, heredity or having a higher PSA level had no detrimental effect on men’s anxiety level when proceeding to biopsy. With older men, anxiety levels overall were lower than those reported by younger men.³⁶⁶ These results are all in complete conjunction with our

findings in **paper II**. The results by both Macefield et al. and ourselves in **paper II** suggest that the screening process for PC affects men's anxiety very little (or moderately in some); even at the biopsy testing stage, and for those men who are aware that they are at greater risk of a positive result.

However, we *do* take note from **paper II** that the proportions of men experiencing "moderate anxiety" were substantial (approximately between 30-40% in all five screening rounds for both the PSA test and the clinical examination). On the other hand, in all cases but the first screening round prior to the first clinical examination, the majority of men reported "no anxiety". It should also be noted that the term for "anxiety" used in the Swedish version of our questionnaire (*sv.* "ångestfyllt") corresponds more to "worry" or "distress" than to real "anxiety", which is more of a psychiatric rather than an item of normal psychological terminology. The psychological, mental or medical impact of "moderate anxiety" should be interpreted carefully.

In **paper II**, we observed a subgroup of men who experienced "severe anxiety" throughout several screening visits. The relative risk of continuing to reporting high levels of anxiety was substantially higher in men reporting a high level in the first screening round. This may reflect the hypothesis that there is a small sub-group of susceptible men with a predisposition to high anxiety levels. The findings are in accordance with those reported from the Rotterdam arm of the ERSPC³¹⁷ in which initial high anxiety levels were maintained during testing. For this subgroup of men, baseline psychological factors may have underlain anxiety and distress levels during the whole screening period. These results are also supported by Brindle et al., who found that men who had higher levels of anxiety before PSA testing also had higher scores at biopsy,³⁶⁵ as well as by Macefield et al. in 2009, showing that psychological mood at PSA testing was predictive of anxiety and distress at later stages of the testing process. Hence, similar to our findings in **paper II**, anxiety seems to be related to the individual. That anxiety seems to affect a sub-group of susceptible individuals has also been reported in breast cancer screening.³⁶⁷⁻³⁶⁹

The finding that there is a subgroup of men who while being investigated for PC may experience anxiety, may not be clinically significant for the individual man. However this information may, firstly, have significance for primary care or preventive medicine physicians or urologists who discuss risk information with men who are making decisions whether to consent to PSA testing (which may lead to a prostate biopsy, which may lead to a diagnosis of PC, which may lead to...and so on). Secondly, this information could be important to include when assessing the potential side-effects from a PC screening program in cost-benefit calculations.

In **paper II**, the PSA level did not influence anxiety levels; neither anxiety levels while awaiting the PSA test result, nor anxiety levels when receiving an invitation to attend clinical examination with prostate biopsies were affected. Thus, in harmony with Roth et al., the PSA level itself does not seem to be a predictor of anxiety, while changing patterns do seem to be. This "PSA-change-anxiety" was indicated in **paper II**, in which we observed that more men reported anxiety while waiting for PSA at repeated

screening as compared to the first screening round (a significant finding in the multinomial logistic regression model, with an OR of 1.49 at repeat screening compared to the first screening round, $p < 0.0001$). We interpreted this as that many men attend screening for reassurance i.e. a man prior to his first invitation assumes his PSA to be normal. When the PSA instead turns out to be abnormal, the awareness of a possible cancer disease becomes evident and affects the level of anxiety in subsequent screening, when a man continues to have elevated PSA levels. This was true for some men, but overall, the majority of men still continued to report “no anxiety” while waiting for PSA, even those with several abnormal PSAs previously.

On the other hand, anxiety associated with biopsy was lower at subsequent screening in **paper II**. The explanation for this is not obvious, but one possible explanation could be that these men had confidence in the care process. On a biennial basis they met a limited number of nurses and urologists. Whether these results would be the same in men with a different cultural background, or with a different screening organization remains unanswered.

In a recent longitudinal report from the ProtecT screening study, anxiety levels throughout the testing process were measured for men with PSA ≥ 3 ng/mL – a design very similar to **paper II**.³⁷⁰ The study finding is reassuring, as most men coped well with the testing process, although a minority experienced elevated distress at the time of biopsy and after a negative result. As seen in **paper II**, psychological state at the time of PSA testing predicted high levels of distress and anxiety at subsequent time-points.

Instruments used to measure short-term outcomes of PC screening have been established in a review and include: State-Trait Anxiety Inventory (STAI), Impact of event scale (IES), Mental Health Inventory, Short Form Health Survey SF-36 or SF-12, and questionnaires developed for the study.³⁷¹ Other suggested questionnaires include the Hospital Anxiety and Depression Scale when measuring screening related anxiety^{365, 372} and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) to identify PC-related anxiety.³⁷³ However, these questionnaires may be too general and not the most sensitive measures for mentally healthy, non-patients to assess fluctuating mood changes in a screening setting. In **paper II**, we used a study-specific/for-study-developed questionnaire consisting of three levels of anxiety: “no”, “intermediate” and “high”. Although it is not a validated psychometric questionnaire, we used the same identical questionnaire throughout the 10 years; it was easy for the screened men to respond to, the response rates were consistently high (~ 90%) and we believe that it assessed what we intended to measure.

The number of men with PSA elevation who accepted clinical examination and responded to the questionnaires was consistently high in **paper II**. There was no relationship between the non-participation rate at the subsequent screening round and the degree of self-reported anxiety at the first round. However, it ought to be mentioned that we do not have information on non-participants who did not attend the first screening round. Did men who refused the first PSA testing, or who did not accept clinical examination, do so because of psychological distress (i.e. there may be a risk of

selection bias)? Essink-Bot challenged the hypothesis of psychological self-selection.³¹⁷ They hypothesized that men with a predisposition to anxiety would be more likely not to respond to a screening invitation. However, they found no difference between attendants and non-attendants, i.e. non-attendants did not have significantly higher levels of anxiety. From the ProtecT study Avery et al. investigated acceptance and decision-making in men accepting, not-responding, or refusing PSA testing and or biopsy³⁷⁴⁻³⁷⁵. They found that men accepting a biopsy had similar scores on the HADS and the SF-12 to those refusing biopsy. Depressed or anxious mood, co-morbidity and LUTS were not associated with the decision to respond to invitations for a PSA test.³⁷⁵

This suggests that in the majority of cases non-attendance is not explained by psychological distress. The high participation rates among men with persistently elevated PSA at repeated screening rounds in the present study might support this. Screening for PC may have a reassurance value, as was reported by Cantor et al.³⁰⁴ Seeking peace-of mind has been reported to be the most important reason for a man to attend PC screening events.³⁷⁶⁻³⁷⁸

In **paper II**, there was no significant correlation between the level of anxiety and family history of PC, a finding consistent with the following previous studies. Taylor et al. reported an increased level of psychological distress prior to PC screening only among men who were also considered to have an elevated perceived risk of the disease, compared to those without a family history.³⁷⁹ Sweetman et al. reported that first-degree relatives attending familial PSA screening do not experience high levels of psychological morbidity.³⁸⁰ Similar results were reported by Bratt et al., who concluded that men with a high hereditary risk of PC do not experience severe negative psychological effects from attendance for screening.³⁸¹ It thus seems that most men with a family history of PC do not experience more anxiety associated with PC screening compared to other men.

The results of **paper II** revealed that levels of anxiety associated with clinical examination were inversely related to age, a finding consistent with screening not only for PC. The adverse psychological impact of screening in relation to younger age has been reported by Brett et al. for mammography screening²⁷³ and by Hughson et al. among women awaiting breast biopsy.³⁸² The same inverse association between age and anxiety has also been observed in women with abnormal cervical smear test results.³⁸³ Suggesting that screening provides reassurance, Taylor et al. showed that PC-related distress, particularly among young men, decreased following receipt of a negative result.³⁷⁹ Among screened men with elevated PSA recalled for biopsy, Brindle et al. found, contrary to the present study, no association between anxiety and age, but found that older men were less anxious than younger men when before the PSA test.³⁶⁵

In **paper II**, there was no correlation between urinary-tract symptoms and anxiety in a multinomial analysis, contrary to the findings of Steginga et al., who reported that men with urologic symptoms at the time of PSA testing were more worried about PC.³⁸⁴ The presence of lower urinary-tract symptoms is common in this age group of men and it seems plausible that symptoms from the urinary tract would be associated with an elevated level of anxiety for PC. As **paper II** comprises as many as 1,781 participating

men one may at least conclude that if such a relationship exists it is weak and is probably not clinically significant.

In **paper II**, we studied the possible influences of age, PSA level, heredity, lower urinary tract symptoms, round of examination, but also biopsy finding. The latter may seem a not intuitively important covariate. However, one might hypothesize that either anxiety levels can affect cancer risk, or alternatively, that men with cancer might be subconsciously anxious. We found no association between biopsy finding and anxiety levels. This finding was confirmed in a recent study from the ProtecT group by Turner et al., where no associations between anxiety and cancer diagnosis were observed. However, as measured by the HADS questionnaire, 'possible' clinical depression was associated with an increased risk of PC, after controlling for urinary symptoms (OR = 1.23; 95% CI=1.01–1.49; p=0.04)³⁸⁵. These findings, the authors stressed, highlight the need for further investigations into the possible role of depressed mental state at the onset of PC and research examining the biological basis for these relationships.

The most stressful aspect of PC screening seems to be waiting for the biopsy result. This has been reported by several authors^{316-317,363,372,386}. In 1995, Gustafsson et al. elegantly explored this longitudinally by measuring serum cortisol as a biological marker for stress at various points during the investigation of men undergoing screening. When compared to a control group of Swedish men during normal daily activity, cortisol levels at the screening examination were higher for screened men, indication that screening per se can create emotional stress. However, two weeks after screening, levels were normal again. Gustafsson et al. further found that the highest levels were found in men who had undergone a prostate biopsy, but were not informed of the result. After they had been informed, cortisol levels fell, regardless of the results of the biopsy.³¹⁶ These findings were confirmed in a structured review by Dale et al. in 2005, in which anxiety appeared to fluctuate over the clinical timeline in response to stressors and uncertainty (such as at the time of screening and/or biopsy), rising before these times and falling afterward.³⁷⁷ These findings imply that the interval between a test and informing the subject of the results should be minimized to decrease the duration of the increased emotional stress.

From **paper II** and the relevant literature, we may conclude that if a PC screening program is introduced, there seems to be no apparent need to introduce special anxiety reducing interventions. We believe that anxiety is not the main barrier to PC screening. However, that high levels of distress may be encountered by some men, should be included in the information presented to men before they consent to undergo a PSA-test.

Discussion

Paper III

This study investigated excess mortality and cause-specific mortality in men undergoing a prostate biopsy among screening participants of the ERSPC. We found no excess mortality during the first year after screening and no deaths directly caused by the biopsy. This low mortality has been confirmed by others.^{254, 320, 329, 387}

To study potential excess mortality, men who have undergone a prostate biopsy need to be compared with men who have not. However, in doing so there is a risk of a selection bias; men who are actually biopsied already constitute a selected group as men who do not undergo biopsy commonly have contraindications to the procedure implying an increased risk of complications, such as bleeding or infection (and potentially death from these complications, or death from co-morbidity or high age). This is the reason why we included not only biopsied men but all men who had a biopsy indication (i.e. screening-positive men).

We found that men who were screen-positive but not biopsied had an increased risk of other-cause mortality up to one year as compared to screen-positive and biopsied men. Our findings therefore suggest, firstly, a “healthy screenee effect” among screen-positive men who attend clinical examination and secondly, a “healthy selection” (by the urologist responsible performing the biopsy) of those who actually undergo biopsies while attending clinical examination.

Our findings are interesting from several aspects, if they are compared with another large-scale population-based biopsy mortality study with similar design, conducted in Canada between 1989 and 2000 by Gallina et al.³⁸⁸ The authors suggested that prostate biopsy might predispose to a higher mortality rate whereas we found that biopsied cases actually had a lower mortality than unexposed men (both screen-positive and screen-negative men). Gallina et al. showed a high overall 120-day mortality after biopsy of 1.3% for 22,175 biopsied men (age range 36 to 101, Md 69 years) as compared to 0.3% for a control group of 1,778 men (aged 65 to 85 years, Md 69.5 years) who did not undergo biopsy. These figures should be compared with 0.24% for our screening-negative group and 0.12% for our screening-positive group who actually underwent biopsy at the same follow-up time. The reasons our result differ can have several explanations. The Canadian population may differ from the European and the settings were different. The Canadian population was included in the Quebec Health plan (clinical data) and patients were in general approximately 5 years older and some very old (up to 101 years), as compared to the present study which emerged from a population-based screening population in which men were younger (range 50.2 – 78.4 years; median 64.8 years for the screening-positive men and 61.2 years for the screening-negative group). In the ERSPC, very few screened men were diagnosed with advanced disease, while the number of men diagnosed with advanced disease in the Canadian study is not presented. Men diagnosed with advanced cancer have an increased mortality rate while men with early disease have not³⁸⁹. To study the association with biopsy it is thus important to include mainly men with non-metastatic disease.

In the paper by Gallina et al., increasing age and co-morbidity were significant predictors of 120-day mortality in multivariate analysis.³⁸⁸ We corroborated the impact of age on mortality, but co-morbidity status was not available in our present screening population. Those who did not undergo a biopsy despite the indication either had co-morbidities or had personal reasons for not wanting to be biopsied. Some men did not show up at all to biopsy and for some men no reason was stated in the biopsy protocol.

However, our findings indicate that men with co-morbidities are less likely to become biopsied in a screening setting, while the selection of men who were actually biopsied in the study by Gallina et al. is not obvious. Whether the rather small control group fully compensates for possible selection of men who were biopsied could be questioned even if co-morbidity status was present in that study (but not among the controls).

However, even though we found no excess mortality associated with prostate biopsy, the procedure is still associated with anxiety for some men, since there may be frequent minor side-effects such as hematospermia and macrohematuria (bleeding from urethra/urinary bladder)⁸⁵ and costs. A recent Canadian study has shown that the hospital admission rates for complications following TRUS-guided prostate biopsy has risen from 1.0% to 4.1% over the last ten years, primarily due to an increasing rate of infection-related complications³⁹⁰. There is therefore a risk, albeit low, of serious complications, although non-fatal. Much research is now being conducted on new markers and nomograms or algorithms for PC screening programs which aim to avoid unnecessary biopsies.

Discussion

Paper IV

This paper is a nationwide population-based record-linkage study showed that the 30-day mortality after radical prostatectomy within the follow-up study in the NPCR and in the linkage with the inpatient register, was low, 0.11% vs. 0.13%, a finding consistent with previous studies based on modern series. A low perioperative mortality is confirmed by others.^{182, 342, 344-345, 391-394} In 2007, the National Board of Health and Welfare regarded this measure as one important quality indicator for PC.⁹ Our study is the first nationwide study from Sweden. The low 30-day mortality found in our study (0.11-0.13%) can be compared with the ethical problem associated with, for example screening, for aortic aneurysms where the peri-operative mortality is estimated at 4-7% (6% after elective surgery in the MASS-study³⁹⁵). In a large randomized trial in the U.K., endovascular repair of abdominal aortic aneurysm was recently reported to be associated with a lower 30-day operative mortality (1.8%) as compared to open surgical repair (4.3%) (however, with up to 8 years of follow-up, no differences were seen in total mortality or aneurysm-related mortality, and endovascular repair was also associated with increased rates of complications and re-interventions).³⁹⁶

Due to increasing diagnostic activity for PC, the numbers of radical prostatectomies performed have increased with time. Concomitantly, the perioperative mortality has decreased. This reduction can probably be explained mainly by improved patient selection, i.e. surgery is more often performed on men who have no co-morbidities. Other explanations attributing to this could be improvements and refinement in surgical technique, anesthesia and perioperative and supportive care.

It has been shown that men selected for radical prostatectomy have a lower mortality than the age-matched background population³⁴⁰. In Sweden, it is not very common for men aged over 70 years to undergo radical prostatectomy²¹⁹. Several authors have

reported that co-morbidity³⁵³ and increasing age are the two most important factors associated with higher risk of perioperative death^{343-344,397}. In one study on radical prostatectomies performed between 1984 and 1990, 30-day mortality for men older than 75 was almost 2%³⁹⁷. However, in 2006, Alibhai et al. called for a rethinking of 30-day mortality with reference to age when reporting that men aged 70-79 years did not have an excess relative risk of 30-day mortality after radical prostatectomy compared with younger men³⁹⁸. In 2004, the same authors had shown that older men were treated with radical prostatectomy less often than younger men with the same remaining life expectancy, even after controlling for co-morbidity. Thus, it has been suggested that there is an age bias in treatment of localized PC, and that this could be questionable, since the relation between age and co-morbidity may be uncertain and fears of treating older men with radical prostatectomy are claimed to be unfounded by some³⁹⁹. Otto et al. explored the risk of cardiovascular mortality in PC patients in the Rotterdam section of the ERSPC. They found that cardiovascular disease was the most common co-morbidity among PC patients. However, compared with all men in the study population with PC, those who underwent radical prostatectomy had the lowest occurrence of cardiovascular disease and were also, on average, younger. This further suggests that there is a selection of healthier patients for surgery⁴⁰⁰.

According to the questionnaires retrieved from the hospitals, the interpretation of the four case presentations is that the deaths were all, somehow, related to the surgical procedure. Three out of the four deaths occurred as a result of acute myocardial infarction. As shown by others, ischemic heart disease seems to be a major risk of death associated with this surgery.^{401, 402, 341} In previous publications, pulmonary embolism has been a common cause of postoperative death,^{401, 403-405} while in the present study there was no such death, at least within 30 days. A more general use of anticoagulants may explain this. However, there is a possibility that thromboembolic complications could still occur after 30 days.

All RPs performed for localized PC at all types of hospital were included in the nationwide study of **paper IV**. The four deaths were considered to be too few to perform an analysis stratified for hospital volume. They occurred at one community hospital, two county hospitals and one university hospital. One death occurred at one of the five high-volume hospitals, which, in total, performed 35% of all radical prostatectomies. Begg et al. found that neither hospital volume nor surgeon volume was significantly associated with surgery-related death (within 30 days). Their overall death rate was 0.5% and was identical for all hospitals³⁵³. Analyzing in-hospital mortality after radical prostatectomy in England, between 1997 and 2004, Judge et al. found that hospitals with the lowest volume of radical prostatectomies had the highest 30-day in-hospital mortality (0.76% for low-volume hospitals compared with 0.30% for high-volume hospitals); however, the finding was based on only 59 deaths, and was further, in multivariate analysis, somewhat attenuated³⁹¹.

Discussion

Paper V

The present report focuses on the self-reported side-effects of the most commonly used curative therapy for men with localized PC – radical prostatectomy – and a comparison between men randomized to screening and the control group. It should be noted that already, before surgery, the prevalence of erectile dysfunction was high for both screened and controls in this population as emerges from a randomized sample from the population. This has been confirmed by others.^{406, 407} In both arms, the majority were sexually inactive or impotent at 18 months postoperatively.

The main limitation of the present study is the relatively small number of evaluable men, and that not all men operated upon provided full and complete answers to all questionnaires. The present study only included men who provided complete answers at both pre and post-treatment assessments. However, we have no reason to believe that this has resulted in a skewed sample of men, thus introducing a potential bias in the results presented. According to a review of the hospital records, non-responders to the questionnaires did not report more unfavorable outcomes. This is further supported by the fact that the actual complications reported by the patients are well in line with the published literature. If anything, the rate of side-effects in the present study was higher than that reported in many other studies.

The not-so encouraging ED outcomes relate in part to the method of presenting data. We calculated impotency not only among men preoperatively potent but also the decrease in function also of men with mild ED preoperatively. Furthermore, presenting frequencies for men reporting several “X” on the IIEF-5 score as “No sexual activity / Did not attempt intercourse”, instead of calculating a total IIEF-5 score where an “X” contributes with 0, is an accurate way of presenting data, since it is not possible to judge whether a man did not attempt intercourse because of erectile dysfunction or any other cause, such as physical distress due to cancer diagnosis, co-existing urinary leakage, or having no partner, et cetera. Using these presumptions, results in lower potency figures compared to what could be the case, if these men are excluded from analysis. Another explanation to the low reported potency rates is the fact that only half of the men in the screening group and less than one third in the control group had a bilateral nerve sparing procedure. Nor was any patient excluded from analysis due to second-line treatment with radiation and/or hormone therapy. Only 3% of men in this population-based study fit into the patient selection published by Parsons et al. in which they reported a 71% postoperative potency after 12 months³⁵⁶. However, in this small subgroup a very much higher potency rate was recorded, in complete harmony with Parsons, 70%. The low postoperative potency rate is in line with other studies on unselected patients found in the literature^{235, 408-412}.

Furthermore, it is worth pointing out that in the present study, erectile function was evaluated at 18 months postoperatively. However, it has been shown that the sexual function can continue to improve even beyond two years postoperatively.⁴¹³⁻⁴¹⁴

For continence, 14.3% of screened men and 20.5% of controls reported some degree of daily urinary incontinence at 18 months post prostatectomy. Most of these men belonged to group “2” which mean they use pads daytime but not necessarily wet. The difference observed between the groups in this study could probably be explained by the difference in the frequency of nerve-sparing operations and stage difference. It has been reported that men who undergo a non-nerve-sparing procedure have a lower chance⁴¹⁵ of regaining, or at least need longer time to regain continence. More severe incontinence (group “4”) was more uncommon but still reported by 2.5 % in the screening group and 2.3 % in the control group.

To the best of our knowledge, **study V** provides the first data available that has attempted to quantify the side-effects of screening based on a truly population-based randomized controlled trial. With 14 years of follow-up, screening reduced PC mortality by 44%, which corresponded to an absolute number of 34/10,000 PC deaths averted. We extrapolated the increased frequency of impotence or sexual inactivity as 120/10,000 men invited and for incontinence 25/10,000 men with screening as compared to no screening. This could thus be interpreted as that for each PC death averted with screening (34/10,000), the surgically induced morbidity because of screen-detected PC will render four (120/34) men impotent or sexually inactive and less than one (25/34) man incontinent. When presented in this way, the number of men with permanent side-effects after radical prostatectomy was low, if related to the number of men saved from PC death.

The present study provides one of the first reports of how an organized, population-based prostate screening program will affect the number of men that will have to live with complications if such a program is introduced. These data can be used when the benefits and harms of PC screening are to be calculated. A limitation is, however, that we have not adjusted for the number of years the men will have to live with these side-effects relative to life-years gained for each PC death averted.

However, we are aware of the fact that these side-effects are not the total population-induced effect of screening, but stem from the most common active treatment option used (80% of cases in the present study). The absolute number of men who received radiation therapy was only slightly higher in the screening compared to the control group in the whole study population (127 versus 82). Radiation therapy in this study will therefore only marginally contribute to the increased burden of long-term side-effects associated with screening. On the other hand there were significantly more men in the control group who received primary endocrine treatment (162 controls versus 80 screened) which will act in the opposite direction, i.e. increase long-term side-effects in the control group.

8. CONCLUSIONS

- PSA screening significantly, and substantially, reduces PC mortality at 14 years of follow-up. Nevertheless, PSA screening is associated with a long and varying lead time, resulting in a risk of over-diagnosis that is substantial but still of a largely unknown magnitude.
- Attending a screening program for PC is seldom associated with severe negative psychological distress, even for men with persistently elevated PSA levels resulting in repeated examinations with prostate biopsies.
- The risk of fatal complications after biopsy of the prostate is low in a population-based screening setting.
- Radical prostatectomy is a procedure with very low perioperative mortality throughout the whole of Sweden (even when performed outside high-volume centers).
- With 14 years of screening, for each PC death averted, the surgically-induced morbidity due to screen-detected PC will render four men impotent or sexually inactive and less than one man incontinent as compared to men who are diagnosed in the clinical setting.

In conclusion, PSA screening significantly, and substantially, reduces PC mortality. This benefit compares favorably to other cancer screening programs. The potential negative consequences of such screening may be acceptable in the light of a disease-specific mortality reduction. The risks of severe consequences from the screening procedures and radical prostatectomy seem minor, but the risk of negatively influencing sexual performance may be substantial. The outcome on a population level may differ from the benefit for the individual.

9. FUTURE PERSPECTIVES

There will never be one study that teaches us everything about the complexities of PSA screening, but the present thesis have given us some clues. We have shown that PSA screening reduces PC mortality by 44% over 14 years, and that the potential negative aspects arising from screening attendance may be acceptable in relation to this disease-specific survival benefit on a population level. The accumulating evidence to date suggests that PSA screening produces a beneficial grade and stage shift, a reduction in advanced disease as well as affording the opportunity to reduce PC mortality.

The 20% PC mortality reduction in favor of screening seen in the ERSPC³⁹, together with the corresponding figure of 44% seen in **paper I** therefore adds some information on what to tell Swedish men who are considering PSA screening. The ERSPC study it was showed, for the first time, that a screening benefit exists. As was already indicated in the Nelson-Aalen curve over cumulative risk of PC death in the ERSPC study (see p.1352, Figure 2 in Schröder et al. *NEJM* 2009;360:1320-8)³⁹, **paper I** in the present thesis now shows us that this benefit increases with longer follow-up. The PLCO trial⁴⁰ could not demonstrate any difference in PC mortality between the trial arms after 7 to 10 years of follow-up (see p. 1314, Figure 1. Panel B in Andriole et al. *NEJM* 2009;360:1310-1319).

Summary of evidence?

Recently, and after the publication of **paper I**, Djulbegovic and colleagues performed a systematic review and meta-analysis of randomized controlled PC screening trials (PSA-based trials, with/without DRE) that was published up to July 2010. Six trials met inclusion criteria, encompassing nearly 400,000 men.⁴¹⁶ The forest plot in figure 18 shows the result of the meta-analysis on effects of screening on death from PC. The authors concluded and signaled to the world media that screening for PC is not supported by evidence as their analysis showed no significant impact on PC mortality.

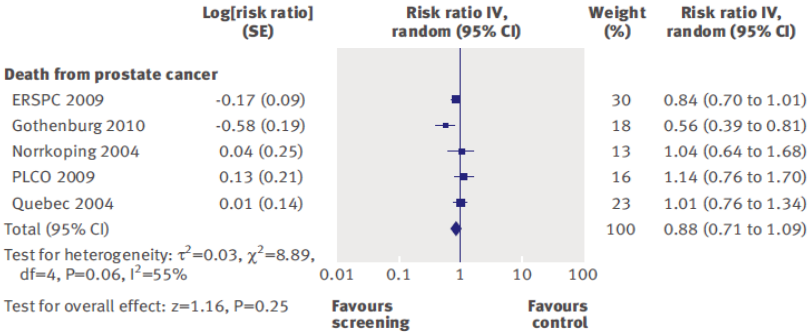


Figure 18. Effects of screening on death from prostate cancer. [Djulbegovic et al. *BMJ* 2010; 341: c4543]

Based on the large study by Djulbegovic et al. should we now reject screening?

Well, let us take a closer look at the figure again. Whether the variability in study results go beyond chance is called heterogeneity. When statistically tested, the p-value was 0.06 and the I^2 was 55%. I^2 values > 50% indicate a moderate to severe level of inconsistency and the results of such an analysis should be interpreted with caution.

However, the Quebec study and the Norrköping study were again included, when in a previous Cochrane review⁹⁶ it was already concluded that these studies had substantial methodological weaknesses. The Norrköping study was primarily designed as a feasibility trial, which is different from studying the clinical outcome mortality.⁹⁹ In the Quebec study, only 23.6% of participants actually complied with the randomization and were screened.⁹⁷ The problem was similar in the PLCO; 30% of men were already pre-screened before the study, and 52% were screened in the control arm by the sixth year.⁴⁰ Therefore, the meta-analysis by Djulbegovic included studies that would not have met eligibility criteria for inclusion had they been predefined. Instead, one could regard this analysis as flawed because of a selection bias when including studies of inadequate quality. To answer the question above: refuting PC screening should not rely on a limited meta-analysis with misleading results, but on evidence from high quality randomized controlled trials together with cost-benefit- and cost-effectiveness analyses.

Preventing the harms of screening

The main harms of PSA screening seem to be over-diagnosis and over-treatment. Future research should be aimed at addressing these issues. **Paper I** in the present thesis informs us that the number needed to be diagnosed in order to prevent one PC death is not as many as previously believed. While it has previously been argued that the balance of benefit against harm for early treatment of PC is not as substantial as it is for other common malignancies, such as breast and colorectal cancer, our results in **paper I**, challenge this. We have shown that the number needed to treat in order to prevent one PC-related death in PC screening is comparable to other screening programs. Furthermore, the numbers may be even fewer, as the identification of PC through PSA-based screening does not have to imply active intervention, but rather management. Kantoff summarized this very well when the ERSPC and PLCO reports were published in 2009: "I do think that there is going to turn out to be a reduction in mortality associated with PSA-based screening, but I also firmly believe that not everybody diagnosed with PC needs to be pigeonholed into a treatment paradigm. And we need to individualize, because clearly there are many patients who are diagnosed with PC that do not need to be treated, who can be observed safely, and will not die of their cancer." In **paper I**, as many as 28.8% of screening attendees were managed expectantly at last follow-up. The concept of active surveillance seems promising for some PCs.

Quality of life and natural history

Any effective screening program, requires more than just effectiveness. More studies are needed on the negative aspects of a screening program, as discussed in this thesis. More

studies are needed on quality of life and cost-effectiveness. While it is accepted that PC is an important public health problem, there is still some paucity of evidence on the natural history of screen-detected disease. More knowledge is needed from modern long-term data for screen-detected tumors from randomized trials, comparing curative treatment options with radical prostatectomy or radiotherapy with the newer active surveillance. Studies on quality of life issues with these different treatment strategies are especially needed.

Aspects on age

Although it was a post-randomization analysis, a recent sub-study of men with no or minimal co-morbidity in the PLCO trial showed a similar decrease in PC-mortality in favor of screening after 10 years of follow-up as that found after 14 years in **paper I**; adjusted hazard ratio 0.56 (95% CI 0.33 – 0.95, $p = 0.03$). The NNT to prevent one PC death was calculated as 5. Men with no or minimal co-morbidity represented more than 1/3 of the study cohort and were younger (median 61 vs. 63 years). The results indicate that selectively screening younger men in good health may reduce the risk of death from PC with a small risk of over-diagnosis and over-treatment.⁴¹⁷

In **paper I**, the median age at study entry was 56 years (range 50-64 years). We noticed that attendees who were older than 60 years at study entry seemed to have a higher risk of dying from PC compared with younger men. Still we are not certain about what age to start and what age to stop screening. Screening should, most probably, be restricted to men <70 years and definitely to men <75 years, who seem to have a very low risk of dying from PC because of co-morbidity and competing risks (and who may only be at increased risk of suffering from serious adverse effects from treatments). As discussed (see above), a single PSA taken in middle age may predict PC up to 25 years subsequently.⁶⁸ It has been suggested by Lilja et al. that if the PSA level taken once at around 40-45 years of age is above the median (corresponding to ≥ 0.65 ng/mL), further PSA testing should be considered with a frequency (annual/biennial/every fourth year) depending on the baseline PSA. For men with levels below the median and no other risk factors, they can consider re-screening at age 55-60.⁶⁷ The PSA test can therefore be used not only to help predict the risk of developing PC, but also to predict the chance of avoiding the disease. Until the time when better markers become available, PSA can be regarded as an appropriate screening tool for PC at a population level.

Screening strategies

A better screening tool more specific for significant tumors is needed. A higher specificity can perhaps be achieved through models that combine the PSA value, the % free to total PSA (F/T PSA), PSA doubling time and previous biopsy outcomes.

For impalpable, silent PC, a blood test can signal cancer, but the diagnosis is made by means of prostate biopsies. In a clinical setting, the decision to proceed to prostate biopsy is mainly based on the PSA level and the DRE finding but also takes into account multiple factors, including F/T PSA, patient age, PSA velocity, PSA density, family

history, ethnicity, prior biopsy history, co-morbidities and absence of contra indications to the biopsy procedure (anticoagulant use, rectal diseases, co-morbidities et cetera). Roobol et al., from the Netherlands section of the ERSPC have shown that using a more individualized approach when deciding to perform prostate biopsies can help reduce potential negative consequences such as unnecessary biopsies (reduced by 1/3 with a PSA cut off level of 3 ng/mL) and detection of indolent disease (reducing PC diagnosis by 13% of which 70-80% were considered as indolent). Very few important PC cases were missed. An individual risk assessment of the screening algorithm was performed by applying a logistic regression model that, in addition to the PSA value, included the transrectal ultrasound picture, the ultrasound volume and DRE.¹¹⁸ It can be discussed whether an individualized approach should be used or whether in a screening algorithm, the indication for biopsy can be simple, such as only a specific PSA cut-off. Perhaps the PSA level needs to be lowered below 3 ng/ml? The optimal indicator/cut-off PSA level for biopsy and the optimal screening interval needs to be established. A screening interval of 8 years might be enough in men with initial PSA levels ≤ 1 ng/ml⁴¹⁸.

There is a need for new sophisticated methods that can predict prognosis (which cancers will most likely be slow-growing as opposed to those will become aggressive). The prognosis can to some extent be calculated from a combination of pre-diagnosis measurements and post-biopsy measurements (histopathology). Nomograms for evaluating the probability of harboring a PC that will show indolent behavior have been developed, including for example PSA levels, ultrasound prostate volume, clinical stage, prostate biopsy Gleason grade, and total length of cancer and noncancer tissue in biopsy cores.^{124, 419} The future will aim at reducing the detection of indolent PC and unnecessary biopsies with more selective strategies.

Shared decision-making

PSA screening emphasises the importance of informed consent. Shared decision-making is crucial. The decision to proceed with screening should always be discussed with the individual, including the benefits and risks of screening, biopsies and treatments. It is essential that the discussion takes place before the screening stage. This may help men considering PSA screening to make quality-decisions. Screening should only be undertaken if a man wishes to proceed. A recent study has indicated that cancer screening decisions reported by patients who discussed screening with their health care providers failed, to a large extent, to meet the criteria for being informed.⁴²⁰ Finding a PC early by means of a screening program, can allow the opportunity for an informed discussion with the patient on the pros and cons of therapy that may otherwise be missed in the absence of routine screening.

There is evidence that treatment for screen-detected PC can cause moderate to substantial harms, especially in those men who would never have developed symptoms during their lifetime. However, the extent to which this is true, should perhaps be left to the individual men to judge? Men have different preferences and values regarding PSA screening. The outcomes of screening, whatever they might be, might not always be in

an individual man's best interest. If a man's goal in life is do to everything possible to minimize the potential risk that a PC will ever harm him, then he should perhaps take the PSA test and either obtain comfort in the knowledge that the test is normal or be treated aggressively in the case of PC that needs treatment (if his remaining life expectancy exceeds > 10 years). However, if a man believes that there are potentially more harm than good to come from screening, he should avoid being tested.

For men with PC, the diagnosis itself, the clinical effects of the disease and its treatment and uncertainties about the future can all take their toll on mental and physical well-being. PC affects not only on the patient, but also his family members and spouse or partner, who may also experience significantly greater psychological distress⁴²¹, but who may consider the eradication of the cancer more important than the QoL effect of treatment side-effects.³⁵⁸

The future

It should be noted, that this far, we have studied only the early effects of PC screening. In **study I**, PC mortality was lowered from 0.90% in the control group to 0.50% in the screening group after 14 years. Of 1,982 deaths in the control group, 78 were due to PC. The lifetime risk for a Swedish man of dying from the disease is 5-6% today. Whether the benefit from screening continues to increase with longer follow-up will be interesting to see and also whether there will be a different balance between the benefits and harms within the upcoming ten to fifteen years. An estimation of the future is difficult to make. Competing morbidity/mortality need to be taken into consideration.

With more extensive observation, we now see that the NNS and NNT have decreased. However, what numbers justify the application of screening on a population basis? The present thesis has described the benefits and the potential negative consequences of PC screening with PSA. But whether the benefits will, at a certain point, outweigh the harms is more of a political and ethical question than a medical one. The limited health-care resources need to be carefully weighed to judge how these should be best spent. Furthermore, the outcome on a population level may differ from the benefit for the individual. There are still uncertainties about the risks of PSA screening, especially the risk of over-diagnosis, over-treatment, and how many years a man needs to live with possible side-effects from treatment before he gains the benefits of screening. One might regard screening as an investment in future health, but as with all investments, there are costs.

The challenges for the future will be to translate the long-term results of the findings of **paper I**, the ERSPC and the PLCO into nationwide population settings. To believe that we will be able to define the precise magnitude of the benefit and a precise schedule for screening is a very high ambition. Breast cancer screening studies have shown that the effect depends on several factors such as age, background mortality and more. What **paper I** has shown is that the benefit from PSA screening could be substantial and much greater than previously believed. This is an important piece of new knowledge but we need more studies in the future to understand all aspects of these complex questions.

Conclusions – where do we go from here?

At the current time point, the results from PC screening studies are promising with regard to the ability to prevent PC death in the male population. However, the step to recommend a general screening in Sweden is not ready to be taken yet. The main reasons for this are:

- A longer follow-up time is still needed to see if the favourable outcome will persist when many men have stopped screening (i.e. too few events in the study at this time point).
- The harms of screening does not always apply to those who benefit from the program which causes an ethical dilemma.
- There are uncertainties regarding the capacity of current health care resources regarding the ability to handle a population-based screening program.

With these points in mind, one could expect a scenario for the next coming years where the new knowledge about PC screening is incorporated in everyday clinical practice in the following way:

- Well informed men, in actual age groups, and without severe co-morbidity should have access to PSA-testing upon request. For men with a confirmed elevated PSA, a referral for urological work-up is recommended.
- Health care providers are recommended to test various models for how a population-based screening program should be organised in the future. This should preferably include some different models including testing via a family doctor or special screening clinics. Pilot projects are ongoing or under way.
- Patient information about the harms and benefits and other consequences of PSA screening needs to be refined and made more accessible to all men, before they make a decision about taking their PSA. This is true irrespective of whether we have the current situation or whether a formal screening program is introduced.

Epilogue

The words of the famous American-born poet and Nobel prize laureate T.S. Eliot (1888 – 1965) will conclude this thesis:

*Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?*

(Choruses from *The Rock*, 1934)

10. Swedish summary (Sammanfattning på svenska)

10.1. Sammanfattning

Denna avhandling utvärderar förhållandet mellan nytta och skada av regelbunden, populationsbaserad screening (=massundersökning) för prostatacancer med blodprovet Prostata-Specifikt Antigen (PSA). Avhandlingen är sprungen ur en prospektiv, populationsbaserad, randomiserad kontrollerad screening studie utgående från Göteborg. År 1995 randomiserades (=lottades) 10,000 män (50-70 år) till PSA screening vart annat år och 10,000 män till kontroller. I avhandlingen ingår fem delarbeten som syftade till att besvara följande frågeställningar:

- I. Kan screening med PSA påverka dödligheten i prostatacancer? Hur stor är risken för överdiagnostik i förhållande till en vinst mätt som sänkt prostatacancerdödlighet?
- II. Upplevs det som ångestfullt när man får besked om förhöjt PSA värde och kallas för vidare undersökning (ultraljud och biopsi) i en screeningsituation?
- III. Diagnosen prostatacancer kan bara ställas med hjälp av vävnadsprovtagning (biopsi) ifrån prostatakörteln vilket sker under vägledning av ultraljud och via ändtarmen. Detta är en invasiv undersökning med viss risk för komplikationer inklusive blodförgiftning. Kan prostatabiopsier vara associerat med en ökad dödlighet?
- IV. Radikal prostatektomi (borttagande av hela prostatan) är den vanligaste behandlingsformen för screeningupptäckt prostatacancer. Hur hög är risken att avlida av operationen?
- V. Radikal prostatektomi är förenat med en tämligen stor risk för impotens och en mindre risk för besvärande urinläckage (inkontinens). I en situation med screening kommer fler män att opereras men samtidigt kan man möjligen operera med skonsammare teknik vid tidigt upptäckta tumörer. Hur många fler män skulle bli inkontinenta och impotenta om screening skulle införas och kan dessa antal sättas i relation till antalet räddade liv i sjukdomen?

Metoder

I delarbete I analyserades skillnaden i prostatacancerdödlighet efter 14 års screening, absoluta och relativa risker beräknades. I delarbete II utvärderades frågeformulär från män med förhöjt PSA med avseende på ångest. Delarbete III är en multi-center studie där även data från screeningstudierna i Holland och Finland ingår och där det studerades om det förelåg någon överdödlighet hos män som genomgick prostatabiopsi (eller hade indikation för detta) jämfört mot dem som inte gjorde det. Delarbete IV är en nationell studie (hela Sverige) där alla män diagnostiserade med lokaliserad prostatacancer och som genomgick prostataoperation (radikal prostatektomi) mellan 1997-2002 identifierades via det Nationella Prostata Cancer Registret (NPCR). Information om 30-dagars-dödlighet efter operation erhöles genom länkning med

populationsregistren. Dödsbevis och frågeformulär från sjukhusen rekvirerades. En validering gjordes via Slutenvårdsregistret. I delarbete V studerades specifikt de som opererades med radikal prostatektomi på Sahlgrenska Universitetssjukhuset och som ingick i en kvalitetssäkringsdatabas. Frekvenserna av impotens före och efter radikal prostatektomi studerades genom ett validerat frågeformulär (IIEF-5) och inkontinens genom ett strukturerat frågeformulär. För män som saknade frågeformulär studerades journaler. Data extrapolerades till hela screening-populationen med 14 års screening.

Resultat

I: Med medellång uppföljning (14 år) så är det en klar skillnad (44%) i prostatacancer-specifik dödlighet till fördel för screening; en effekt som är bättre än för bröstcancer-screening med mammografi och screening för kolorektalcancer. I absoluta tal är minskning emellertid liten, 0,40%, vilket motsvarade att 293 män PSA-testades i 14 år för att ett dödsfall i prostatacancer skulle undvikas. För varje förebyggt dödsfall hade också 12 fler cancerfall diagnostiserats i den screenade gruppen jämfört med kontrollgruppen.

II: 1781 män med förhöjda PSA svarade på frågeformuläret i första omgångens screening. Av dessa rapporterade 66% ingen ångest av att vänta på PSA-provsvaret medan 2% rapporterade att det var mycket ångestfyllt. Ångestnivån ökade med upprepade undersökningar, även om majoriteten fortsatte att rapportera "inte ångestfyllt". Att bli kallad för vidare klinisk undersökning med biopsier var associerat med ingen ångest i 45%, medan 6% upplevde detta som mycket ångestfyllt. Med upprepade undersökningar samt med ökande ålder minskade ångestnivåerna.

III: Ingen överdödlighet sågs till följd av prostatabiopsi hos mer än 12,000 biopserade män jämfört med män som inte biopserats. I världslitteraturen beskrevs ett fåtal ovanliga fall med dödlig utgång av biopsi till följd av svår infektion (blodförgiftning).

IV: Av 3,700 utförda prostataoperationer (radikala prostatektomier) ingående i uppföljningsstudien i NPCR var 30-dagars-dödligheten 0.11%. I samtliga fyra fall, som förekom på tre olika typer av sjukhus, var dödligheten sannolikt relaterad till operationen. Av samtliga 4,457 män opererade enligt slutenvårdsregistret (oavsett ålder, tumörstadium, PSA etc.) under samma tidsperiod var motsvarande siffra 0.13%.

V: Radikal prostatektomi var den vanligaste kurativt syftande terapin. Majoriteten var impotenta eller sexuellt inaktiva 18 månader efter operationen. Eftersom fler tumörer upptäcktes i screeninggruppen blev också fler män impotenta och inkontinenta i denna grupp, men relativt sett sågs en tendens till en lägre andel biverkningar i denna grupp. Screeningen förhindrade också död i sjukdomen. Satt i relation till denna vinst var antalet män med biverkningar få; för varje förhindrat dödsfall efter 14 år, hade fyra män blivit impotenta och mindre än en man blivit inkontinent ("kostnaden per räddat liv").

10.2. Kortfattade slutsatser

I: PSA screening ger en säkerställd minskning av dödligheten i prostatacancer och effekten verkar större än den man ser vid mammografi, men priset är överdiagnostik.

II: PSA screening är sällan associerad med upplevelse av svår ångest, även för män med förhöjda PSA-nivåer resulterande i flera kliniska undersökningar med prostatabiopsier.

III: Risken för fatal utgång efter prostatabiopsi är mycket låg i populationsbaserad PSA screening.

IV: Radikal prostatektomi är en säker operation med mycket låg operationsrelaterad dödlighet i hela Sverige (även utanför sjukhus med högst operationsvolym).

V: Satt i relation till varje förhindrat dödsfall i sjukdomen efter 14 års screening, är frekvenserna av impotens och inkontinens förhållandevis låga för män med screening-upptäckt prostatacancer jämfört med kliniskt upptäckta cancrar. För den enskilde mannen kan dock biverkningarna vara betydande.

Sammanfattningsvis har denna avhandling visat att masstestning med blodprovet PSA kan halvera dödligheten i prostatacancer. Denna fördel är jämförbart bättre än vad man sett i andra cancerscreening-program. De potentiellt negativa konsekvenserna av sådan screening kan vara acceptabla i ljuset av den sänkta dödligheten i sjukdomen. Allvarliga komplikationer av screening-procedureerna samt av prostataoperationer (radikala prostatektomier) är ovanliga, men risken att negativt påverka den sexuella förmågan är betydande. Utfallet för en hel population kan också skilja sig från vinsterna för den enskilde mannen.

Framtiden?

Vid denna tidpunkt är resultaten av screeningstudier lovande vad gäller att förhindra prostatacancerdöd i den manliga befolkningen. Ännu är dock tiden inte mogen att rekommendera allmän PSA-testning då kunskaperna om skada visavi nytta ännu inte är tillräckliga. De män som erfar biverkningar av screening har inte nödvändigtvis samtidigt nytta av densamma, vilket innebär ett etiskt dilemma. Vi behöver fortfarande längre uppföljningstid och mer kunskaper. Vi vet ännu inte säkert om det finns resurser inom svensk hälso- och sjukvård att hantera följderna av en allmän PSA-testning. Sjukvårdshuvudmän rekommenderas därför att pröva olika modeller för att studera hur information och inbjudan till screening accepteras samt hur screening kan organiseras i primärvård och/eller via speciella screeningkliniker. För män med förhöjt PSA-värde rekommenderas uppföljning hos urolog. Patientinformationen bör revideras/uppdateras och göras tillgänglig till alla män innan de beslutar sig för att ta sitt PSA, så att såväl risker (nackdelar) som möjliga vinster (fördelar) lyfts fram. *Välinformerade* män i den aktuella åldersgruppen och utan samsjuklighet bör inte nekas PSA-testning.

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13. APPENDICES

13.1. Original screening questionnaire (in Swedish)

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Sahlgrenska Universitetssjukhuset

UROLOGI

Tacksam om Du kunde fylla i nedanstående uppgifter. Alla Dina svar kommer att behandlas konfidentiellt och när alla svar är inkomna, kommer resultatet att avidentifieras.

Ringa in lämpligt alternativ.

Har Du några allvarliga sjukdomar som Du behandlas av läkare för? I så fall, vilka?

.....
.....

Har Du behandlats för någon tumörsjukdom? I så fall vilken?

.....
.....

Har Du tidigare undersökt Dig avseende prostatacancer?

1. Ja
2. Nej
3. Vet ej

Har Du några släktingar med prostatacancer?

1. Ja, i så fall vem?
2. Nej
3. Vet ej

Har Du haft problem med vattenkastningen i form av dåligt flöde eller svårt att tömma blåsan?

1. Inte alls
2. Lätta besvär
3. Avsevärda besvär

Har Du problem med vattenkastningen i form av täta trängningar?

1. Inte alls
2. Lätta besvär
3. Avsevärda problem

Forts.

Har du upplevt problem med minskad sexuell lust?

1. Inte alls
2. Lite problem
3. Avsevärda problem

Har Du upplevt besvär med minskad sexuell förmåga?

1. Inte alls
2. Lite problem
3. Avsevärda problem

Hur upplever Du möjligheten att delta i den aktuella studien avseende prostatacancer?

Ringa in mest lämpliga svar.

1. Som en förmån
 2. Brukar ställa upp i olika undersökningar och därför var det naturligt.
 3. Blev rekommenderad av någon annan att delta
 4. Deltager mot min vilja, men vågar ej låta bli.
 5. Annan orsak, var god ange vad
-

Upplever Du det ångestfyllt att vänta på svaret efter blodprovet?

1. Inte alls
2. Lite ångestfyllt
3. Mycket ångestfyllt

Hur upplever Du det att få kallelse för läkarundersökning?

1. Inget särskilt
2. Lite ångestfyllt
3. Mycket ångestfyllt

TACK FÖR DIN MEDVERKAN!

13.2.1. The International Index of Erectile Function-5 questionnaire

The IIEF-5 questionnaire^a

Over the past six months:					
	Very low	Low	Moderate	High	Very high
1 How do you rate your confidence that you could get and keep an erection?	1	2	3	4	5
2 When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
3 During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most time (much more than half the time)	5 Almost always/always
4 During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	1 Extremely difficult	2 Very difficult	3 Difficult	4 Slightly difficult	5 Not difficult
5 When you attempted sexual intercourse, how often was it satisfactory for you?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always
	1	2	3	4	5

^aThe IIEF-5 score is the sum of the ordinal responses to the five items; thus, the score can range from 5 to 25.

13.2.2. IIEF-5, modified from Rosen et al. (as used in paper V)

1 How do you rate your confidence that you could get and keep an erection?	-	1 Very low	2 Low	3 Moderate	4 High	5 Very high
2 When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	X No sexual activity	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the times)	4 Most times (much more than half the time)	5 Almost always/always
3 During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	X Did not attempt intercourse	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most time (much more than half the time)	5 Almost always/always
4 During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	X Did not attempt intercourse	1 Extremely difficult	2 Very difficult	3 Difficult	4 Slightly difficult	5 Not difficult
5 When you attempted sexual intercourse, how often was it satisfactory for you?	X Did not attempt intercourse	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most time (much more than half the time)	5 Almost always/always

13.2.3. Frågeformulär sexuell funktion, "ED-score" (In Swedish)

Varje fråga har 5 svarsalternativ. Dessutom finns i de flesta fall ytterligare en kolumn med ett kryss (X) som Du ringar in om frågan inte är relevant för Dig. Ringa in det svar som bäst beskriver Din situation. Ringa endast in ett svarsalternativ per fråga.

EREKTION		Mycket svag eller ingen alls	Svag	Måttlig	Stark	Mycket stark
1. Hur uppskattar Du att Din tilltro till att kunna få och behålla en erektion varit de senaste 3 månaderna?	-	1	2	3	4	5
2. Hur ofta efter sexuell stimulering har Din erektion, under de senaste 3 månaderna, blivit tillräckligt styv för att kunna tränga in i Din partner?	Ingen sexuell aktivitet har förekommit	Nästan aldrig eller aldrig	Några få gånger (mycket färre än hälften av gångerna)	Ibland (ungefär hälften av gångerna)	De flesta gångerna (mycket mer än hälften av gångerna)	Nästan alltid eller alltid
	X	1	2	3	4	5
3. Hur ofta har Du, under samlag, kunnat behålla erektionen sedan Du trängt in i Din partner de senaste 3 månaderna?	Inga försök till samlag har förekommit	Nästan aldrig eller aldrig	Några få gånger (mycket färre än hälften av gångerna)	Ibland (ungefär hälften av gångerna)	De flesta gångerna (mycket mer än hälften av gångerna)	Nästan alltid eller alltid
	X	1	2	3	4	5
4. Hur svårt hade Du att behålla erektionen ända till slutet av samlaget de senaste 3 månaderna?	Inga försök till samlag har förekommit	Mycket stora svårigheter	Stora svårigheter	Svårigheter	Vissa svårigheter	Inga svårigheter
	X	1	2	3	4	5
TILLFREDSSTÄLLELSE	Inga försök till samlag har förekommit	Nästan aldrig eller aldrig	Några få gånger (mycket färre än hälften av gångerna)	Ibland (ungefär hälften av gångerna)	De flesta gångerna (mycket mer än hälften av gångerna)	Nästan alltid eller alltid
5. När Du de senaste 3 månaderna försökt genomföra samlag, hur ofta har Du upplevt dem som tillfredsställande?	X	1	2	3	4	5

Total ED-poäng (fr 1-25): _____

6. Är Du Gift/sambo
 Ensamboende men med fast relation
 Ensamboende
7. Om Du angett att Du är sexuellt aktiv – hur ofta upplever Du orgasm?
 Aldrig
 Någon enstaka gång
 Ungefär hälften av gångerna
 Mer än hälften av gångerna
 Alltid eller nästan alltid
8. Använder Du något potenshjälpmedel (läkemedel eller annat hjälpmedel)?
 Aldrig Ibland Oftast Alltid
 I så fall, vilket?.....

13.3. Questionnaire assessing urinary incontinence (as used in paper V)

Värdering av vattenkastning

Har Du urinläckage?	<input type="checkbox"/> Aldrig 0	<input type="checkbox"/> Läcker ibland vid hosta, nysning eller använder droppskydd vid speciell fysisk ansträngning, t ex sportaktivitet, trädgårdsarbete 1	<input type="checkbox"/> Droppskydd hela tiden (utom möjligtvis nattetid) men de är inte alltid våta 2	<input type="checkbox"/> Droppskydd hela tiden som måste bytas pga. att de är våta 3	<input type="checkbox"/> Läcker kontinuerligt och behöver blöjor som kontinuerligt bytes 4
---------------------	---	--	--	--	--

Do you have urinary leakage?	<input type="checkbox"/> Never 0	<input type="checkbox"/> Sometimes urinary leakage when coughing or sneezing / sporadic use of pads associated with physical exertion such as sports, gardening et cetera 1	<input type="checkbox"/> Regular use of pads (except sometimes at night), but they are not always wet 2	<input type="checkbox"/> Regular use of pads that need to be changed because they are wet 3	<input type="checkbox"/> Constant urinary leakage that requires diapers to be changed continuously 4
------------------------------	--	---	---	---	--

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