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# Individualized Prostate Cancer Testing - Men's views on participation

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## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To all the women in my world,

*Education is aimed at helping students get to the point where they can think on their own*

- Noam Chomsky

# ABSTRACT

Prostate cancer (PCa) is the second most common cancer in men in the world and the fourth most common occurring cancer overall. However, because the harms from testing with prostate-specific antigen (PSA) are considered to outweigh the benefits, no governmental body has yet adopted a PSA-based screening program. Risk-based screening could potentially help reduce the proportion of men undergoing biopsy by identifying individuals at the highest risk of developing PCa, and thus reduce the harms of overdiagnosis and overtreatment. However, little is known about the psycho-social aspects surrounding risk-stratified PCa testing.

This thesis, and the papers encompassed, aims to increase knowledge regarding men's views on participation to individualized prostate cancer testing (PCT). Their interest in partaking in a risk-based PCT as well as its effect on their psycho-social health were investigated. A better understanding of their views, as well as predictors of participation and aspects of invitation would help inform development of population-based PCa screening programs to optimize attendance.

By using a cross-sectional survey in **Paper I**, the objective was to explore the general population's interest in, and acceptability of, the prospect of risk-stratified cancer screening programs. A representative sample of 10.000 individuals (20-74 years of age) were invited to respond to a web-survey with questions developed by a panel of experts. Men were asked about PCa screening and women were asked about breast cancer screening.

Out of our 2822 respondents (28%), a vast majority (94%) showed interest in wanting to know their cancer risk, with men presenting more certainty than women. A total of 87% agreed to the concept that if identified with a high risk, they would get screened more often. Only 27%, however, would agree to get screened less often if identified as having a low risk.

**Paper II**, **Paper III** and **Paper IV** studied actual participation in risk-based PCT. The PCa test was conducted within the frame of the STHLM3 trial, a large study for men 50-69 years of age in the region of Stockholm (Sweden). STHLM3 aimed at validating a risk-based PCT model in order to identify high-risk PCa. By participating in STHLM3, men were communicated their PCa risk (low, intermediate or high).

The study sample in **Paper II** represented a sub-sample of 28.134 men invited to the pilot study of STHLM3. They were randomly allocated to different survey design factors in order to investigate optimization of participation rates. The study sample for **Paper III** and **IV** was

also nested in STHLM3 and consisted of 10.000 men. They were invited to respond to a web-survey concerning worry, knowledge, health behavior and attitudes, as well as health related quality of life, three months before STHLM3, at invitation to STHLM3, and five months after participation in STHLM3.

**Paper II** and **Paper III** investigated predictors of participation to the risk-based PCa screening program. **Paper II** investigated survey and invitation design predictors (the use of a pre-notification, the length of the invitation letter, the length of the questionnaire and the use of a reminder or not). **Paper III** examined psycho-social predictors (worry, knowledge, health behavior and attitudes, and health-related quality of life) for participation in PCT.

The participation rate in **Paper II** was 34%. The use of a pre-notification and a reminder increased participation to STHLM3. In **Paper III**, 1915 men responded to the questionnaire three months before invitation to STHLM3. When comparing decliners of STHLM3 (30%) with participants to STHLM3 (70%), participants presented more worry and an increased level of vulnerability, as well as a better general health than decliners.

Finally, almost 1000 men responded to the psycho-social questionnaire three months before STHLM3 as well as five months after STHLM3, enabling examination of the impact over time of participating to the risk-based PCT in STHLM3. Men assigned to a low or intermediate risk level reported that the levels of worry decreased over time, whereas men assigned to a high-risk level reported no increased level of worry. A low level of PCa knowledge was observed throughout **Paper III** and **IV**, calling for improved effort on that front before introducing PCa screening.

Although participation rates could still be optimized, if implemented risk-stratified screening has the possibility to be accepted by the general public. Moreover, the study revealed no negative impact on the well-being of men participating in risk-based PCa testing.

# LIST OF SCIENTIFIC PAPERS

I. Koitsalu, M., Sprangers, M., Eklund, M., Czene, K., Hall, P., Grönberg, H. & Brandberg, Y. **Public interest in and acceptability of the prospect of risk-stratified screening for breast and prostate cancer**. Acta Oncologica, 2016, 55:1, 45-51.

II. Koitsalu, M., Eklund, M., Adolfsson, J., Grönberg, H. & Brandberg, Y. **Effects of pre-notification, invitation length, questionnaire length and reminder on participation rate: a quasi-randomised controlled trial**. BMC Medical Research Methodology, 2018, 18:3

III. Koitsalu, M., Eklund, M., Adolfsson, J., Sprangers, M., Grönberg, H. & Brandberg, Y. **Predictors of participation in risk-based prostate cancer screening**. PLoS ONE, 2018, 13(7): e0200409

IV. Koitsalu, M., Eklund, M., Adolfsson, J., Sprangers, M., Grönberg, H. and Brandberg, Y. **The STHLM3-model, risk-based prostate cancer screening, identifies men at high risk without inducing negative psychosocial effects** (manuscript submitted to European Urology).

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADT | Androgen deprivation therapy |
| ANCOVA | Analysis of Covariance |
| CAP | Comparison Arm for ProtecT |
| CRiSP | Cancer Risk Prediction center |
| DRE | Digital rectal examination |
| EORTC | The European Organisation for Research and Treatment of Cancer |
| ERSPC | European Randomized Study of Screening for Prostate Cancer |
| GP | General practitioner |
| hK2 | Human kallikrein 2 |
| HRQoL | Health related quality of life |
| ISUP | International Society of Urological Pathology |
| mpMRI | Multi-parametric magnetic resonance imaging |
| PCa | Prostate cancer |
| PCT | Prostate cancer testing |
| PLCO | Prostate, Lung, Colorectal and Ovarian |
| ProtecT | The Prostate testing for cancer and Treatment |
| PSA | Prostate-specific antigen |
| SARA | Survey About Risk Assessment |
| SNP | Single nucleotide protein |
| S3QOL | Stockholm-3 Quality of Life |
| SPAR | Statens personadressregister [The State's personal address registry] |
| STHLM-3 | Stockholm-3 |
| TRUS | Transrectal ultrasound-guided |
| TNM | Tumor, nodes, metastasis |
| USPSTF | U.S. Preventive Services Task Force |
| UTI | Urinary tract infection |

# 1 INTRODUCTION AND FOREWORD

In 2008, a 10-year Linnaeus grant, financed by the Swedish Research Council, enabled the development of a Centre of Excellence at Karolinska Institutet focusing on Cancer Risk Prevention. The Cancer Risk Prediction Center (CRiSP) was born on a shared vision to decrease the mortality of breast and prostate cancer by focusing on individualized cancer risk prediction and prevention. Compared to traditional project funding targeting a single principal investigator for a few years at most, the 10-year duration of the Linnaeus grant as well as the size of the funding allowed researchers to think bigger. CRiSP's steering committee consisted of 11 professors from Karolinska Institutet and the Karolinska University Hospital, from both pre-clinical and clinical departments, covering together a vast array of scientific fields. The long-term strategy to reach their vision was based on building the largest and best-characterized cancer cohorts in the world (1, 2).

Through a lucky chain of events, I was introduced to Yvonne Brandberg in 2010. Yvonne is by profession a clinical psychologist as well as a professor in Care Science with a focus on Oncology. She was one of the 11 professors on CRiSP's steering committee and I immediately fell in love in her projects touching upon psycho-social aspects of individualized cancer screening. It felt like it was marrying perfectly my biomedical background with my nursing training.

This thesis is compiled of three published papers and a manuscript all centered around individualized prostate cancer testing (PCT) and men's views on participation to PCT. I believe it is important to keep in mind that as a society, our assumptions and pre-conceived notions constantly evolve and what might have seemed an ambiguous notion years ago might sound like an obvious concept today. The idea of personalizing medicine has come a long way in ten years and has progressed from mere discussion to a self-evident concept. The views and opinions stated by our participants and measured in our studies are reflections of the society's progress in the matter at that moment in time. When moving from a "One-size-fits-all" screening regimen to prevention involving knowing one's cancer risk it is important to keep the recipients in mind. CRiSP's efforts would have been worthless if the recipients in the end did not want to know or could not cope with their cancer risk. Therefore, it was important to ask the general population how they felt about possibly knowing their cancer

risk likelihood (at the fear of possibly discovering that they did not want to know it!) as well as to attempt to measure the impact of individualized PCT on several psycho-social aspects. In simpler term, one could say that we performed a market analysis of risk-based PCT.

Alaska, 2020-07-22

# 2 BACKGROUND

## 2.1 PROSTATE CANCER

### 2.1.1 Epidemiology and etiology

The prostate is an exocrine gland in men below the urinary bladder and located in the upper part of the urethra. The word prostate comes from latin *prostata; pro-* "before" and *-sta* "to stand" due to its position at the base of the bladder (3). Its function is to produce a thin secretion which contributes to the volume of the semen at ejaculation. The alkalinity of the prostatic fluid prolongs the lifespan of sperms by neutralizing the acidity of the vaginal tract. Dihydrotestosterone, a metabolite of testosterone, predominantly regulates the prostate. Many studies have shown a pattern of prostatic growth with age (4, 5). However, changes in prostate size are highly variable among aging men (6). Disorders of the prostate include prostate cancer, benign prostatic hyperplasia (enlarged prostate), and prostatitis (inflammation).

In Sweden, prostate cancer (PCa) is the most common cancer and represent 16,3% of the total number of diagnosed cancer cases (7). Approximately a third (31,2%) of all cancers in men are prostate cancer. In 2016, 10.474 men were diagnosed. Median age at diagnosis is 70 years. One out of eight men is at risk of developing prostate cancer before the age of 75 (7). The median age of death from PCa is 80 years. Two-thirds of all men who die of PCa are older than 75 years (8). Prostate cancer is found at obduction or during bladder cancer surgery in men without known previous PCa diagnosis in approximately a third of men in their 60's, and in half of the men in their 80's (9, 10). Autopsy studies of men who died of other causes have revealed that more than 20% of men aged 50-59 years and more than 33% of men aged 70-79 years had prostate cancer (11). Thus, not all men with prostate cancer experience symptoms. PCa screening is therefore important. More on this later in chapter 2.2.

The actual cause of PCa is still unknown, but some risk factors have been identified. First and foremost, PCa incidence is strongly related to age. PCa is very uncommon in men younger than 45, but becomes more frequent with increasing age (12). Although an environmental influence on the development of PCa is presumed, an important part is played by genetic predisposition. Men who have a first-degree relative with PCa have twice the risk of

developing PCa. Moreover, men with two first-degree relatives with PCa have a five-fold greater risk compared to men with no family history (13). Twin studies in Scandinavia suggest that 42 percent of the risk may be explained by heritable factors (14). Moreover, differences in PCa incidence and mortality between white and Afro-american men (156 resp. 25 in white vs. 248 resp. 59 in Afro-american men/100.000 men) (15) points to this genetic aspect. Although the incidence appears to be lower among Chinese and Japanese men, Japanese men who have migrated to the US have a higher incidence compared to men still living in Japan (16), reinforcing the idea that the environment play an important role.

### 2.1.2 Prostate cancer investigation procedures in Sweden

In the region of Stockholm (17), the following symptoms are indications for suspicion of PCa and should give rise to further investigation in form of a prostate-specific antigen (PSA) test and prostate palpation:

- Rapidly increasing urinary disorders (last six months)
- Increasing skeletal pain
- Skeletal metastases without known primary tumor
- General cancer symptoms such as fatigue and loss of appetite.

A referral to a urologist for investigation of PCa should be sent if:

- Men < 70y: PSA ≥ 3 ng/mL
- Men 70-80y: PSA ≥ 5 ng/mL
- Men > 80y: PSA ≥ 7 ng/mL
- And/or: suspicion of malignancy at prostate palpation.

Asymptomatic men who asks for a PSA test should be offered The National Board of Health and Welfare's brochure about pro and cons regarding PSA-testing. Men with less than 15 years of life expectancy should be dissuaded from PSA-testing. Men with more than 15 years of remaining life expectancy (note: average mortality in men in Sweden is 87 years) who want prostate cancer testing (PCT) can be offered PSA-tests according to the following recommended test intervals:

- If under 65 years and PSA < 1ng/mL, test every 6 years
- If over 65 and PSA < 1ng/mL, discontinue testing
- If PSA 1-2,9 ng/mL, test every 2 years until they reach 75 years

- If an increase of > 1ng/mL since last test, take a new test after one year
- Men with low testosterone (<8mmol/L) should be tested every 2 years

And finally, if belonging to a hereditary risk group (i.e. men with two or more family members with PCa before 75 years or known mutation in gene BRCA2 or HOXB13), a referral should be sent when PSA ≥ 2ng/mL.

### 2.1.3 Diagnosis

The use of prostate-specific antigen (PSA) test, digital rectal examination (DRE) and core biopsy is the recommended way to diagnose PCa in Sweden (18).

#### *2.1.3.1 Prostate-specific antigen test*

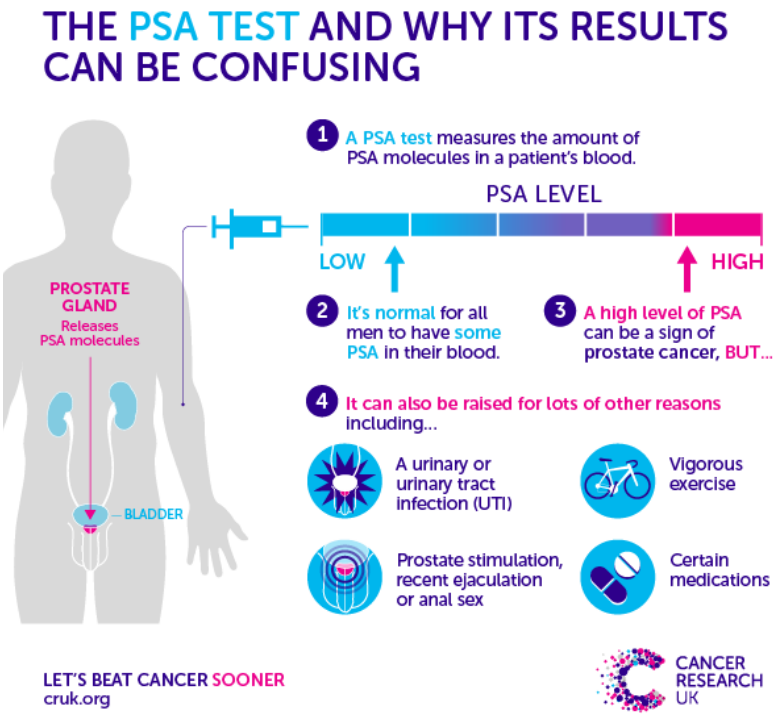
PSA is a protein made by cells in the prostate gland and is mostly found in semen, but a small amount can also be detected in blood. A number of conditions can cause an elevation in PSA levels but the three most frequent ones are prostate cancer, prostatitis (inflammation) and benign prostatic hyperplasia (enlarged prostate). All of those conditions of the prostate can interfere with the natural barrier of cells between the intraductal prostatic fluid and capillaries and thus worsen PSA leakage into blood causing an elevated PSA level. Moreover, PSA levels also tend to increase with age. It is believed this is due to a deterioration over time of the glandular structure, facilitating PSA to leak into capillaries. That is why PSA values are difficult to interpret. PSA levels may vary over time in the same man and there is no specific normal or abnormal level of PSA in the blood. Most men without PCa have PSA levels under 4 ng/mL of serum. Men with a PSA level between 4 and 10 have a 1 in 4 risk of having PCa. If the PSA is above 10, the risk of having PCa is over 50%. But some men with PSA levels below 4.0 ng/mL have PCa and some men with higher levels do not have PCa (19)

Some tumors grow so slowly that they are unlikely to lead to death. When those tumors, that are not life-threatening, are detected it is called “over-diagnosis” and thus treating these tumors is called “over-treatment”. About 25% of men who have a prostate biopsy due to an elevated PSA level are found to have PCa following a biopsy. (20)

While it is normal for men to have some PSA in their blood, a raised level can be a sign of PCa. But PSA can be raised for many other reasons too, leading to an abnormal PSA result despite no presence of cancer (false-positive result). As mentioned earlier, inflammation and/or enlargement of the prostate can cause elevated PSA. A urinary infection can cause very high PSA-levels. It can take up to a year for the value to drop back to normal levels. Acute urinary retention also increases PSA-levels. And finally, because PSA production is dependent on testosterone, men with hypogonadism (diminished functional activity of the gonads) can have an advanced PCa despite low PSA-values.

Other aspects that can affect the PSA-value are sample management for example. The way the blood sample is handled can affect the PSA value. For example, the ratio of free/total PSA decreases if the sample is being left for more than 3 hours without being centrifuged or cooled. Moreover, there is a variation of approximately 5% between different laboratories in Sweden.

Figure 1. The PSA test




Credit: Cancer Research UK

#### *2.1.3.2 Digital rectal examination*

A digital rectal examination (DRE) is an internal examination of the rectum to, in the case of PCa suspicion, palpate the surface of the prostate gland to assess its texture, shape, size and tenderness. Although being simple and complication-free, it is subjective since it is dependent on the examiner (21). Although commonly used to screen for PCa, its benefits have been disputed (22). The US Preventive Task Force do not recommend DRE as a first-line method of PCa screening due to the lack of evidence supporting its efficacy (23). In Sweden, DRE is still performed (18)

#### *2.1.3.3 Prostate biopsy*

When PCa is suspected, a prostate biopsy is performed. The clinical judgment to proceed with a prostate biopsy depends on risk factors such as age, PSA-levels, DRE findings, a positive family history of PCa, previous prostate biopsy, and the patient's life expectancy (24). However, diagnosing PCa cannot be performed without a biopsy and is based on the microscopic assessment of prostate tissue obtained via needle biopsy. A biopsy can be performed transperineally or transrectally. The most common method is transrectal ultrasound-guided (TRUS) biopsy. In a systematic fashion, 10-14 cores are taken from different regions of the prostate gland in a grid-like pattern. Although systematic, it is a method that misses a quarter of PCa (25). Since approximately 2005, multi-parametric magnetic resonance imaging (mpMRI) has been used to better identify and characterize prostate cancer (26). Prostate cancers missed by conventional biopsy are detectable by MRI-guided targeted biopsy (27). Indications for targeted biopsy include for example patients for whom traditional TRUS biopsies have been negative despite concern for rising PSA (28).

One of the most frequent complication of prostate biopsies is bleeding (hematuria, hematospermia, rectal bleeding) (29) and varies with factors such as prostate size, anticoagulative medication, and number of biopsy cores taken (30). Approximately, 3% of cases require hospitalization due to infectious complications (bacteriuria, urinary tract infection, epididymitis, meningitis, sepsis) (31). Prostate biopsy is also associated with significant pain, discomfort, and anxiety (32). Those side-effects represent the physical harms when screening for PCa and are the reasons why unnecessary biopsies should be avoided.

#### *2.1.3.4 Grading and staging of prostate cancer*

In order to choose the most appropriate type of treatment, the cancer will be staged and graded. Staging is to determine its size and eventual spread to other parts of the body whereas grading describes the cancer cells. The most commonly used staging system is the TNM classification. TNM stands for Tumor, Nodes and Metastasis and aims at describing the size of the tumor, its spread to lymph nodes and the existence of metastases.

For many years, the Gleason scoring system has been used by pathologists for grading the biopsy samples and issues a primary Gleason grade for the predominant histological pattern and a secondary grade for the highest pattern. They are both based on the microscopic architecture and appearance of the cells and represent a scale of 1 to 5 and are being added to each other to get a Gleason score sum. In 2014, a consensus conference revised pathological grading into 5 strata called the International Society of Urological Pathology (ISUP) score (33, 34). This new grading system was incorporated into the 2016 World Health Organization classification of tumors, and has gradually been introduced since then.

For men diagnosed with localized PCa, clinicians stratify the diagnosis in low, intermediate and high risk of progression to determine the most appropriate course of treatment. The risk is determined by combining biopsy grading, clinical staging and pre-biopsy PSA levels

In Sweden, the risk groups are defined as follow (18):

- Low risk cancer: T1-T2a, Gleason score sum ≤ 6 and PSA < 10ng/mL
- Middle risk cancer: T2b and/or Gleason score of 7 and/or PSA 10-19.9ng/mL
- High risk cancer: T3-4 and/or N1 and/or M1 and/or Gleason score sum 8-10 and/or PSA ≥ 20 ng/mL

Figure 2. Risk prognosis in relation to ISUP grading score and Gleason score

| Risk Group | ISUP Grade Group | Gleason Score |
|---|---|---|
| Low | Grade Group 1 | Gleason Score ≤ 6 |
| Intermediate Favorable | Grade Group 2 | Gleason Score 7 (3 + 4) |
| Intermediate Unfavorable | Grade Group 3 | Gleason Score 7 (4 + 3) |
| High | Grade Group 4 | Gleason Score 8 |
| High | Grade Group 5 | Gleason Score 9-10 |

Credit: Prostate Cancer Foundation (pcf.org)

### 2.1.4 Management

For men diagnosed with PCa, several management options exist. The precision in identifying and characterizing PCa tumors has increased over time and allows clinicians to stratify patients by risk and to recommend therapy based on patient preference and cancer prognosis. The treatment course depends on the cancer risk stage.

For men with low-risk PCa, active surveillance has become the recommended approach (35) because those cancers are expected to grow slowly. Active surveillance (or active monitoring) tries to avoid or delay unnecessary treatment by monitoring the disease progression. It requires regular monitoring and curative treatment is offered if/when the cancer gets worse over time. Active monitoring has its pros and cons. By undergoing active monitoring, patients can potentially avoid eventual side-effects of curative treatment methods (such as erectile, rectal and urinary dysfunction) but may suffer from psychological aspects from living with untreated cancer and the fear of disease progression (36). A UK-based study, The Prostate testing for cancer and Treatment (ProtecT) trial, showed that active monitoring is as effective as surgery and radiotherapy in terms of survival at 10 years (37). Moreover, the same trial showed no differences between the different treatment groups (active monitoring, radiotherapy, and surgery) in terms of anxiety, depression and health-related quality of life (38). Moreover, a systematic review performed in 2014 concluded that men on active surveillance report good levels of well-being and do not suffer major negative psychological impacts (39).

Men diagnosed with localized disease (no lymph nodes or distant metastases) and with a PSA > 10 ng/mL and palpable nodule during DRE are offered surgery and/or radiation. PCa treatment side effects include, among others, erectile dysfunction, urinary issues, incontinence, and can diminish men's quality of life. Finally, the first-line treatment for metastatic PCa continues to be androgen deprivation therapy (ADT).

## 2.2 PROSTATE CANCER SCREENING

The World Health Organization (WHO) defines screening as a process that begins with invitation to participate and ends with treatment for appropriately identified individuals. The practice of screening is an important mode of cancer prevention and early detection. The objective of early detection and prevention of cancer is to decrease, reverse or eliminate one's risk of developing and dying of cancer (40). Primary prevention mechanisms (e.g., increased physical activity, changes in diet, tobacco cessation, use of sunscreen, etc.) can reduce the impact of exposures to factors that could induce cancer. Secondary prevention strategies, such as cancer screening, allow for the early detection of precancerous lesions or help inhibit, or even reverse, cancer progression. Tertiary prevention methods are used to help keep a localized cancer from spreading or metastasizing (40). Recent advances in the field of cancer have pushed cancer prevention to incorporate molecular knowledge and risk stratification profiles to allow screening regimens to be matched to one's risk of cancer (40).

In 1968, the WHO commissioned a report from Wilson and Jungner asking them to define screening criteria in order to guide the selection of conditions that would be suitable for screening (41) (see Box 1). Due to advances in genetic screening, those screening criteria were revised in 2008 (42) (see Box 2).

**Box 1. Wilson and Jungner classic screening criteria**

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment 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.

**Box 2. Synthesis of emerging screening criteria proposed over the past 40 years**

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

Reprinted from Bulletin of the World Health Organization, 86 (4). Andermann, A., Blancquaert, I., Beauchamp, S., & Déry, V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years, pp 317–319. Copyright (2008).

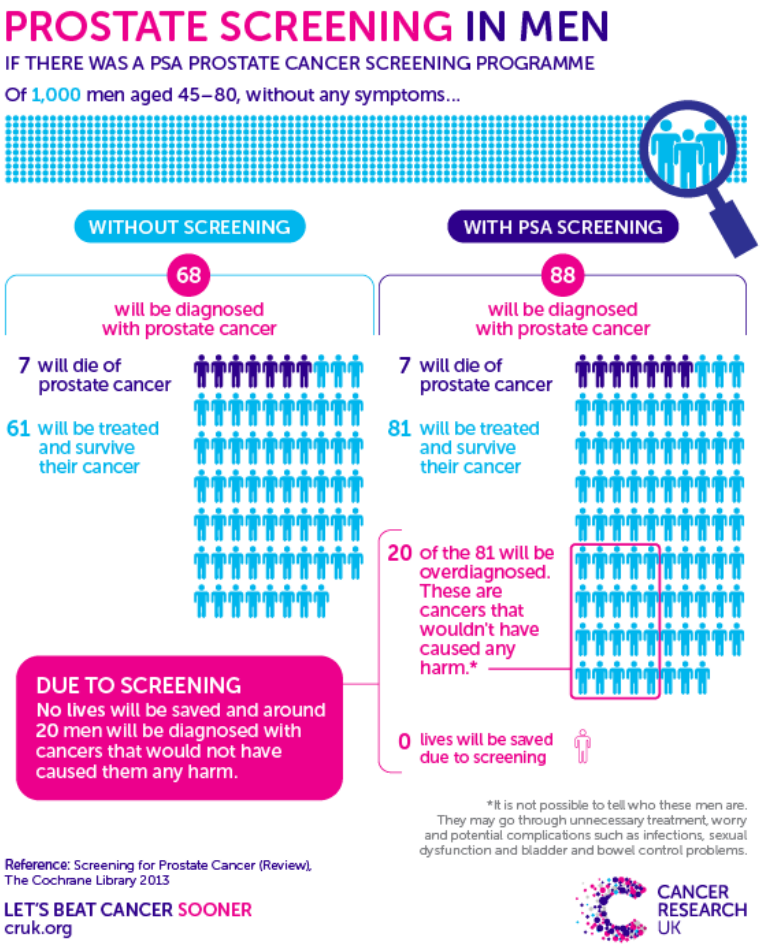
This thesis will add knowledge relating to several criteria needed to be met for prostate cancer screening to become an organized screening program. As Wilson and Jungner mention in their report, the test should be "acceptable to the population". This will be discussed further on. Moreover, as suggested by Andermann et al. the screening program should "integrate education" and "ensure informed choice". Those aspects will also be discussed in this thesis.

### 2.2.1 The screening situation of today

In November 2018, the Swedish National Board of Health and Welfare (*Socialstyrelsen*) decided that PCa screening with PSA-test should not be offered to men in the 50-70 years of age range (43). The same year, the U.S. Preventive Services Task Force (USPSTF) made a similar conclusion and decided to recommend against PSA-based screening for PCa in men 70 years and older; and for men aged 55 to 69 years, the decisions to undergo PCa screening with PSA test should be made on an individual level (23). The main reason behind those

decisions is that the harms associated with PSA screening outweigh the benefits. Up to now it has been difficult to distinguish indolent PCa from potentially fatal PCa without recourse to invasive detection methods. When these slow-growing harmless cancers are found, they are said to be 'overdiagnosed'. A Cochrane review (44) came to the conclusion that prostate-cancer screening with PSA did not significantly decrease PCa specific mortality.

Figure 3. Prostate screening in men




Credit: Cancer Research UK

Despite, those recommendations, >50% of all Swedish men aged 55-69 year have undergone a PSA test (45). However, PCT takes place even if it is not recommended. This is done based on the recommendation of individual physicians or by request of the patients. Godtman et al. (46) showed that organized PSA screening seems more effective than opportunistic screening. Compared to men offered an organized biennial screening program, unorganized screening resulted in more overdiagnosis.

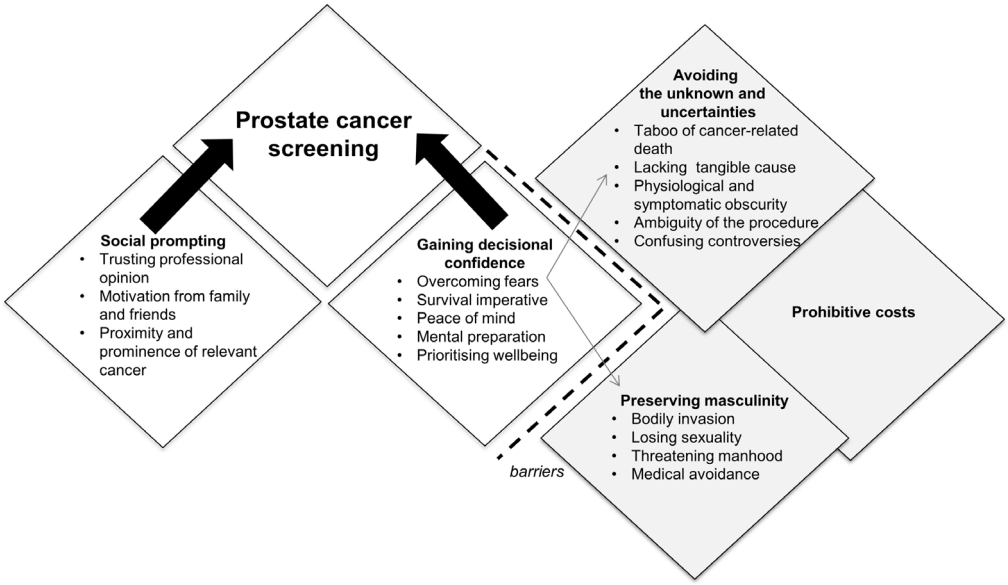
### 2.2.2 Ongoing international trials

The European Randomized Study of Screening for Prostate Cancer (ERSPC), in which Sweden participates, is a multicenter, randomized trial of screening for PCa of 162.388 men. About 900 PCa deaths have so far been recorded (47). The control arm consists of the usual care with no screening and the intervention arm is based on PSA testing every 2-4 years. The latest update showed that the absolute risk reduction of death from PCa at 13 years was 1.28 per 1000 randomized men (47), thus confirming that PSA testing can lead to a considerable reduction in PCa mortality. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large randomized trial designed and sponsored by the National Cancer Institute (NCI) in the US. One of the objectives was to determine whether screening men with DRE and PSA can reduce mortality from PCa by randomizing men to an intervention arm or a control arm (48). The PLCO trial indicated no reduction in PCa mortality. (49) But after accounting for differences in implementation and settings, it was shown that the ERSPC and PLCO provided compatible evidence that screening reduces PCa mortality (50). The ProtecT trial, a UK-based trial, aims at investigating the effectiveness of treatments for localized PCa by randomly assigning men to active monitoring, radiotherapy, or surgery (51). The ProtecT trial showed that active monitoring is as effective as surgery and radiotherapy in terms of survival at 10 years (37). The CAP (Comparison Arm for ProtecT) Randomized Clinical Trial comparing men aged 50 to 69 years undergoing one single PSA screening vs controls not undergoing this procedure, found that a single PSA screening intervention detected more low-risk PCa cases but had no significant effect on mortality after a median follow-up of 10 years (52).

### 2.2.3 Men's perspectives on prostate cancer screening

The controversies concerning prostate cancer screening highlights a consensus that informed decision making is of utmost importance when a man is to decide upon participation in prostate cancer screening. In 2017, a systematic review summarized men's attitudes and perspectives of PCa screening (53) and presented the following figure:

Figure 4. Thematic schema of conceptual links among themes on men's perspectives on prostate cancer screening




Credit: James et al. Men's perspectives of prostate cancer screening: A systematic review of qualitative studies. *PLoS One*. 2017;12(11):e0188258. Published Nov 2017. doi:10.1371/journal.pone.0188258

The review concluded that men are interested in participating in prostate cancer screening in order to prevent cancer and gain reassurance about their health. Fears of losing their masculinity, acceptance of the intrusiveness of screening and the ambiguities about the necessity were some of the obstacles that needed to be overcome for them to go ahead and proceed with PCa screening.

A qualitative study by Rai et al. also investigated influences on men's decision to have a PSA test (54). The results suggest that the patient's mind is already made up by the time he sees his GP, thus emphasizing the importance for the information about the pros and cons of PSA testing to reach men before visiting their GP:

> "*Men wanted to be tested primarily because they believed in the benefits of early diagnosis. Triggers for consulting the GP were the personal experiences of friends with prostate cancer, a desire to be proactive about health, media reports, a family history or ongoing urinary symptoms. Before consulting the GP, men's awareness was largely based on personal accounts and media stories and did not include much familiarity with the potential limitations of testing. Many had decided they wanted to be tested by the time they consulted their GP and this decision remained largely unaffected by the consultation. Men varied in the value they placed on receiving information about the benefits and limitations of PSA testing from their GP*." (54)

Men undergoing PSA testing did not show any significant increase in anxiety, even with an abnormal PSA result in one study (55). However, those with a disposition to anxiety experienced higher levels of anxiety than others throughout the screening process (55). A prospective questionnaire nested within the UK based ProtecT study confirmed that men receiving an abnormal PSA result did not experience increased anxiety and depression levels (56). However, men with a benign biopsy have been shown to be concerned about PCa (57, 58). The Gothenburg section of the ERSPC reported anxiety associated with PCa screening to be low to moderate, even in men with elevated PSA (59). Anxiety affected a smaller group of men only. Anxiety when awaiting PSA results were only influenced (increased) if they had previously had elevated PSA tests. (59)

In the Rotterdam section of the ERSPC trial, PCa screening participants did not experience considerable short-term impact on health related quality of life (HRQoL), despite short-lasting side effects related to prostate biopsy (55) The results from the Finnish arm of the ERSPC supported that finding by concluding that short-term HRQoL effects of PCa

screening were minor and transient (60). Finally, a systematic review from 2011 concluded that screening does not appear to have long-term negative emotional impacts (61).

## 2.3 INDIVIDUALIZED CANCER SCREENING

Several studies have suggested public acceptance for population-based risk-stratified cancer screenings (62-64). However, changing today's cancer screening regimens to individualized screening based on risk will highlight the importance of educating potential screening recipients. Potential recipients will need to understand and be educated around the subtleties of risk:

> *"Recipients or potential recipients of screening become responsible for developing an appropriate sense of their risk status and therefore eligibility for screening. Lower-risk groups acquire responsibility for developing a sense of proportion around their expectations, whilst higher-risk groups are required to be more vigilant"* (65).

The ProtecT feasibility study demonstrated that when using age-base thresholds of PSA levels to indicate abnormality, approximately 10% of men aged 50-70 years will have a raised PSA level, and about 70% of those will be false-positives (66). The PLCO cancer screening trial showed that trial adherence was poorer among those who had received previous false-positive results (67). This emphasizes the importance of personalizing PCa screening by risk-stratification to increase avoidance of false-positives.

### 2.3.1 Improving PSA testing

During the last decade, additional tests that could complete the picture given by a PSA test have been developed. The added tests are aiming at reducing the number of men needing to undergo biopsy and thus decreasing overdiagnosis.

One method being tested is multi-parametric magnetic resonance imaging (MP-MRI). MP-MRI can be used to triage men with high-serum PSA to avoid unnecessary TRUS-biopsy, and therefore avoid side-effects from the biopsy. According to Ahmed et al (68) mpMRI,

when used before prostate biopsy to triage the men, could reduce unnecessary biopsies by a quarter.

Siddiqui et al. (69) studied targeted prostate biopsies, that is biopsies using a fusion of MRI and ultrasound, and found that they could increase the detection of high-risk PCa.

New molecular biomarkers that classify tumor aggressiveness have also become available. By using biopsy tissue, different gene assays can tell more about the patients' prognosis (70-72).

## 2.4 THE STHLM3 PROJECT AND S3QOL STUDY

### 2.4.1 Aim

The purpose of the Stockholm 3 (STHLM3) project was to develop and validate a risk-based PCa testing model (the STHLM3 model) in order to identify high-risk PCa (with a Gleason score of at least 7) with better test characteristics than that provided by PSA testing alone. The primary aim was to increase the specificity compared with PSA alone without decreasing the sensitivity to diagnose high-risk PCa (2). In other words, decrease the number of unnecessary prostate biopsies and reduce overdiagnosis without compromising the ability to diagnose high-risk PCa compared to PSA alone.

### 2.4.2 Method

The STHLM3-model consists of a combination of plasma protein biomarkers, genetic markers, clinical variables, and a prostate exam. In addition to total PSA, the other plasma protein biomarkers were selected based on a systematic scientific literature search as well as two subsequent validation studies using the STHLM2 cohort. On that basis, free PSA, hK2, intact PSA, beta-microseminoprotein (MSMB) and macrophage inhibitory cytokine-1 (MIC-1) were selected due to their (substantial) correlations with the presence of Gleason Score ≥ 7. Moreover, based on literature search and genetic assessment in several studies, 254 single nucleotide proteins (SNPs) were selected based on their association with PCa (73-75). Finally, clinical variables (age, family history, previous prostate biopsy), and a prostate exam (digital rectal exam and prostate volume) were selected based on their association with PCa risk.

STHLM3 was a prospective, population-based diagnostic study of men without PCa aged 50-69 years from Stockholm, Sweden. The study followed a paired screen positive design, where two tests (PSA alone and STHLM3 model) were performed on each study participant. The men were randomly invited by date of birth from the Swedish Population Registry kept by the Swedish Tax Agency. Men with PCa at enrollment were excluded from the study. The invitation included:

1. An invitation letter with brief information about the study
2. A study information brochure with comprehensive information about the study and reference to the STHLM3 website (www.sthlm3.se) for additional information
3. A combined referral and consent form with three questions on family history, one question on previous prostate biopsy and one question about current use of certain medication
4. A list of 67 laboratories in Stockholm participating in STHLM3.

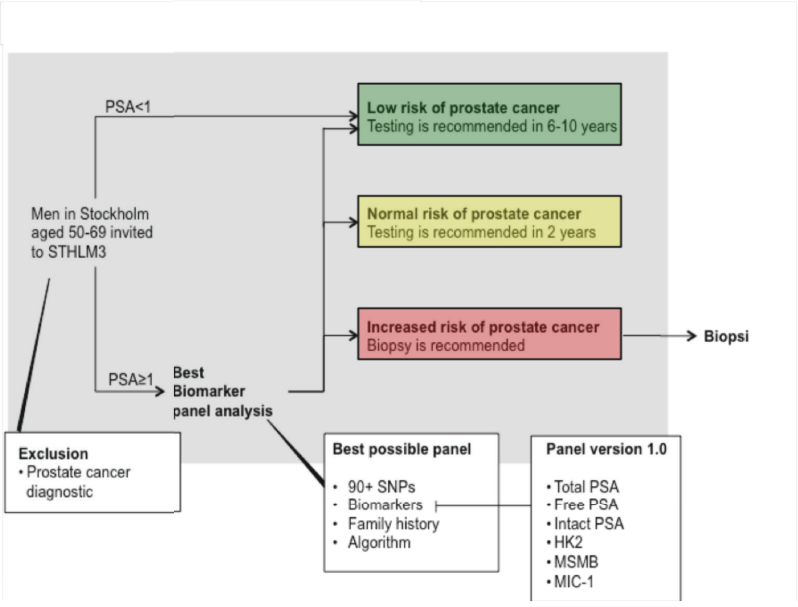
Those who chose to participate in STHLM3 were also invited to respond to a more extensive web-survey. The survey covered demographics, medical history, bladder specific questions, use of alcohol and tobacco, diet, physical activity, and use of selected drugs. A subset of the men was also asked to respond to psycho-social questions within the Stockholm 3 Quality of Life ("S3QOL") study. Data from this subset of questionnaires form the basis of two of the papers in this thesis (paper III and IV).

PSA levels were analyzed in all participants. Men with a PSA concentration of less than 1 ng/mL were excluded from being tested with the additional biomarkers from the STHLM3 model. Men with a PSA of at least 3ng/mL or the STHLM3-model result indicating high risk were considered to be at an increased risk of PCa and were referred to a urologist (see Figure 5).

Each participant received a response letter by mail based on the results of the PSA test or STHLM3 model. The letter provided one of the following three recommendations: (1) "Low risk" with the recommendation to perform a new test in six years; (2) "Normal risk" with the

recommendation to have a new test in two years or (3) "Increased risk" of PCa with the recommendation to consult a urologist for further examination. The urologist performed DRE, prostate volume measurements, and transrectal biopsy.

Figure 5. STHLM3's design




### 2.4.3 Results

A total of 145.905 men aged 50-69 years from Stockholm were invited to the STHLM3 study as part of the training cohort in May 2012 – May 2013 or the validation cohort Aug 2013 – Dec 2014, and approximately 40% of them participated in STHLM3. The STHLM3 model performed better than PSA alone for detection of cancers with a Gleason score of at least 7. Without compromising the ability to diagnose high-risk PCa, the STHLM3 model could reduce unnecessary biopsies when compared to a PSA test with a cutoff of ≥ 3 ng/mL. The STHLM3 model could reduce the number of biopsies by 32% and avoid 44% of benign biopsies (2).

### 2.4.4 S3QOL

Nested in STHLM3 was the prospective psychosocial study, S3QOL. The aim was to focus on psychosocial and quality of life-aspects surrounding STHLM3. For this, a total of 10.000 men planned for invitation to STHLM3 were asked to respond to a set of questionnaires pertaining to PCa worry, PCa knowledge, attitudes and health behavior, HRQoL, PCT specific distress, and biopsy specific distress. They were asked to respond to the questionnaires in S3QOL at three points in time: (T1) three months before invitation to participation in STHLM3, (T2) at the time of their invitation to participate in STHLM3, and (T3) five months after participation in STHLM3 (see Figure 6). The prostate cancer test specific distress questionnaire and the biopsy specific distress questionnaire were not used in the papers encompassed in this thesis and will therefore not be described in more details.

Figure 6. Questionnaires used at different time points for S3QOL

| Themes | T1 | T2 | T3 | References |
|---|---|---|---|---|
| Prostate cancer worry | ☑ | ☑ | ☑ | Steginga et al., 2001; Katz et al., 2007; Watson et al., 1999 |
| Health related quality of life | ☑ | ☑ | ☑ | Aaronson et al., 1993; van Andel et al., 2008 |
| Knowledge about prostate cancer | ☑ | ☑ | ☑ | McNaughton-Collins et al., 2004 |
| Attitude and health behaviour | ☑ | ☑ | ☑ | Avery et al., 2012 |
| Prostate cancer test specific distress | ☐ | ☑ | ☑ | Taylor et al., 2002; Macefield et al., 2010 |
| Biopsy specific distress | ☐ | ☐ | ☑ | Taylor et al., 2002; Macefield et al., 2010 |

# 3 AIM

There has been a push towards individualized PCa screening as a means to reduce the harms of PCa screening. Before implementing a new screening method, like here a risk-based PCa screening, it is important to assess whether the general population is interested in knowing their risk and using that new method for individualized screening intervals. It is also important to examine if and how that new method affects those invited. Better understanding of men's views on participation in individualized prostate cancer testing (PCT) will help inform the development of population-based screening programs. The overarching aim is to increase knowledge concerning men's views on participation in individualized PCT to help policy-makers in their decision to implement public prostate cancer screening.

The center of our focus lies in individualized PCT. "Individualized" is used interchangeably throughout the thesis with personalized, risk-based, and risk-stratified. The emphasis is specifically upon men's views on participation to PCT.

The specific aims of the studies are as follows:

**Study I**: To explore the interest in and acceptability of the prospect of individualized prostate cancer testing and mammography screening.

**Study II**: To examine factors in the invitation to PCT (pre notification, invitation letter, and reminder) to optimize participation in PCT.

**Study III**: To examine, three months before invitation to participation in PCT, factors of importance for participation in PCT (PCa worry, knowledge of PCa, attitudes towards PCT and health related quality of life (HRQoL)).

**Study IV**: To investigate if there were differences between the risk groups five months after participation in PCT in terms of worry, knowledge, attitudes and HRQoL, and to examine changes over time in these variables.

# 4 FUNDING

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# 5 METHODS

## 5.1 STUDY DESIGNS AND CONTEXT

Through our four studies we have looked at three different time aspects surrounding PCT.

The first time point consisted of taking a picture of a moment in time. The aim was to describe individuals' interest in or attitudes towards individualized cancer screening in a large sample of the population. Thus, **Paper I** is a cross-sectional study that measures men's' and women's' opinion and views to the prospect of risk-stratified screening for PCa and mammography, respectively. The study was conducted a few years before individualized PCT was carried out through STHLM3.

The second time aspect represents the papers leading up to PCT, i.e. upstream of PCT. Their goals were to give a picture of various predictors for participation in PCT. In **Paper II**, factors that affect men's participation from a methodological aspect were investigated. This is an experimental prospective study where the investigator intervenes in multiple ways to affect the outcome. **Paper III** is an observational prospective longitudinal study designed to examine psycho-social predictors of PCT, carried out three months before the invitation to participate in STHLM3.

Finally, the third time aspect in this thesis is reported in **Paper IV** in which the downstream effects of PCT participation on men are examined prospectively from before invitation to five months after participation in STHLM3.

## 5.2 STUDY SAMPLE AND PROCEDURES

### 5.2.1 The SARA-study

"SARA" stands for "Survey About Risk Assessment". A total of 10.000 individuals between 20 and 74 years of age were randomly selected from the Swedish population, collected from the SPAR registry. They were selected to match the age and sex distribution of the Swedish population as registered in 2009. The participants were contacted via a mailed letter and asked to login to a web-survey. The women were asked about their opinions concerning the prospect of individualized mammography whereas the men were asked about individualized PCa screening. The invitation letter's heading introduced the subject by asking the following question: "Would you like to influence future mammography/prostate cancer screening?".

The letter then went on to elaborate the concept of risk-stratified screening and subsequent individualized screening program. The letters were mailed in November 2011 and data was collected until January 2012. Within this thesis, the emphasis will be upon the results of men's interest in individualized prostate cancer testing. However, for the sake of comparison, the men's results will be discussed against the women's results, and their views on the prospect of individualized mammography screening.

A sub-sample of 300 persons who did not participate in the survey was randomly selected for telephone interviews in order to study reasons for non-participation. Respondents were asked two questions: their reason(s) for not participating and if they would want to know their breast/prostate cancer risk.

### 5.2.2 The STHLM3 pilot-study

The study sample examined in **Paper II** was embedded in the pilot study for STHLM3 and was conducted to test for optimal survey design and procedures for data collection in order to achieve maximum participation to PCT through the STHLM3-trial. In the fall of 2012, during six consecutive weeks, invitations were mailed out to a total of 28.134 men, 50-69 years of age, living in the region of Stockholm, without previous prostate cancer diagnosis. The men were randomly selected by date of birth from the Swedish Population Registry in a quasi-randomized fashion and allocated to receive: (a) a pre-notification postcard or not; (b) a shorter or a longer invitation letter; (c) a shorter or a longer web-based questionnaire; and (d) a reminder or not. The allocation patterns were combined into six study arms. Men who chose to join the STHLM3 were also invited to respond to a more extensive web-based questionnaire. The questionnaire covered demographics, bladder specific questions, medical history, use of selected medicines, use of alcohol and tobacco, diet, and physical activity. For the purpose of this thesis, we will focus on the impact the different methodological survey designs had on participation in PCT, but not on participation in the STHLM3 questionnaire. Studying how to increase participation to epidemiological questionnaires is an interesting and important aspect of research, but is not the focus of this thesis.

### 5.2.3 The S3QOL-study

S3QOL stands for "STHLM3 Quality of Life" and is a study sample that was nested in the STHLM3-trial. The study sample for S3QOL consists of a sub-sample of 10.000 men of the invited STHLM3 study population. Psycho-social aspects were studied at three time-points surrounding STHLM3: (1) Three months before being invited to STHLM3, (2) alongside participation to STHLM3 and, (3) five months after participation to STHLM3. In January 2014, 10.000 men who were due to be invited to participate in STHLM3 three months later, received an invitation to complete a web-survey. The web-survey covered four main psycho-social areas: (A) PCa-specific worry and perceived vulnerability; (B) Knowledge about PCa; (C) Attitudes and health behavior towards PCT; and (D) Health-related quality of life (HRQoL). That same web-survey was inserted in the STHLM3 questionnaire for the men to complete if/when they participated in STHLM3. Finally, in September 2014, an invitation was sent asking the men to fill out the same web-survey. The S3QOL study sample is described in **Paper III** and **IV**.

## 5.3 OUTCOMES AND INSTRUMENTS

### 5.3.1 The SARA questionnaire

The questionnaire used in **Paper I** was developed by a panel of clinical, psychological, and epidemiological experts. Pilot interviews with 20 healthy women and 10 healthy men were conducted according to the EORTC guidelines for questionnaire development (76). This was done to ensure the cultural and linguistic integrity of the questions. A pilot study was carried out on a random sample of 200 women from the Swedish population in order to test the web's functionality and the study logistics. The final questionnaire consisted of two parts: (A) Public interest in cancer risk and underlying reasons (3 items), and (B) Public acceptability of the prospect of risk-based screening (7 items). The response alternatives were given on a four-point Likert scale and ranged from Absolutely/Agree to Definitely not/Disagree. For some items the option 'Neither' was added. The original questionnaire was developed in English and translated into Swedish by a professional translation agency. An English version of the questionnaire can be found in the Supplementary content of **Paper I**.

### 5.3.2 STHLM3-pilot study

The outcomes measured in **Paper II** were the proportion of completed web-based questionnaires, the proportion of men who performed PCT by providing blood within STHLM3, and the proportion of participants who completed both. The focus in the thesis remains on the relationships between the four different survey design aspects studied in the pilot study (pre-notification, length of invitation letter, length of questionnaire, and reminder) and the proportion of men who actually participated in PCT.

The pre-notification consisted of a postcard describing the upcoming invitation to participate in STHLM3 and was sent one week ahead of time. The information provided in the invitational package consisted of an invitation letter with, at the back of it, a checklist explaining the procedure for giving blood in the PCa testing, as well as an extensive brochure with in-depth information about STHLM3. The difference between the short and long invitation letter consisted in the number of words on the first page of the letter. The long version was twice as long as the short one. An English version of the letters can be found in the Supplementary material of **Paper II**.

Those who belonged to an intervention arm where a reminder was included were sent one two weeks after receiving the invitation letter, regardless of whether they had already participated or not.

Men who choose to participate in STHLM3 were also invited to respond to a more extensive web-based questionnaire. The questionnaire was not a mandatory aspect of PCT. Its sole purpose was to collect data for different research projects in relation to STHLM3. In the pilot-study, two versions of the questionnaire were tested. A short one consisting of 500 items and a long one consisting of 1000 items.

### 5.3.3 S3QOL study

S3QOL consisted of questionnaires covering six different areas. Four of those were used in **Papers III** and **IV:** Worry, Knowledge, Attitudes and health behavior, and HRQoL. The items used in our questionnaires have been used in previous international PCa studies. They were translated into Swedish by a certified translator.

#### *5.3.3.1 Prostate cancer specific worry and perceived vulnerability*

The worry-questionnaire consisted of six items adapted from items used previously in different studies (58, 77, 78). The items and response options can be found in **Paper III**.

#### *5.3.3.2 Knowledge about prostate cancer*

The six-item questionnaire used in S3QOL to measure PCa knowledge was previously developed and used by McNaughton-Collins (79) for men without a prostate cancer history. The items and response options can be found in **Paper III**.

#### *5.3.3.3 Attitudes and health behavior*

A questionnaire was developed for a study with the aim to identify predictors of attendance for PCT and prostate biopsy (Avery et al., 2012). The questionnaire consists of 26 items comprising six domains: (A) Perceived threat of developing prostate cancer (2 items), (B) Perceived benefits of PCT (8 items), (C) Perceived barriers to PCT (10 items), (D) Intentions to undergo PCT (1 item), (E) External influences on PCT decision making (3 items), and (F) General health (2 items).

#### *5.3.3.4 Health-related quality of life*

To measure HRQoL The EORTC Quality of Life Core Questionnaire (QLQ-C30) version 3 was used. This is a cancer-specific questionnaire consisting of 30 items. It incorporates five functional scales (physical-, role-, cognitive-, emotional- and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting), and a global health and quality of life scale. For the latter scale, responses range from 1 (“Very poor) to 7 (“Excellent”), whereas the response options for the other scales are scored with 4-point scales ranging from 1 (“Not at all”) to 4 (“Very much”). The EORTC QLQ-C30 has been widely used in cancer-related settings since the 1990’s when it was first developed (80). The Swedish version of the older core instrument (EORTC QLQ-c36) has shown overall validity (81) and there is reference data from the Swedish population (82).

## 5.4 STATISTICAL METHODS

### 5.4.1 Preparation of item scores and analysis

In **Paper I**, in order to test for possible differences between respondents and non-respondents, a Kolmogorov-Smirnov test was conducted on the age distribution and a chi-square test on the sex-distribution. To test for differences according to sex, age-group and education, Chi-square tests were performed.

For **Paper II**, participation rates between the different arms were compared by performing Chi-square tests with a significance level set to 0.05.

In **Paper III**, ordinal categorical data (such as found in the worry and knowledge questionnaires) were analyzed using Fisher's exact test. For analysis consisting of comparing population means (as in the Attitude and HRQoL questionnaires), independent Student t-tests were performed. The level of significance was set to 0.05.

For the "Attitudes and health behavior" questionnaire, we added the possibility for participants to respond 'Do not know'. Items in each scale were summed only if half or more of the responses in the scale were not composed of the response item "Do not know". Summary scores were produced for each scale.

For the EORTC QLQ-C30 questionnaire, all scales were linearly transformed ranging from 0 to 100. The nausea and vomiting symptom scale as well as the single-items, with the exception of "Pain", are not reported in this paper as we did not consider them pertinent to this study.

For **paper IV**, the response options for the Worry and Knowledge questionnaires were dichotomized. Wilcoxon signed rank tests were used to test for evidence of association between baseline and follow-up within a risk-group. Analysis of Covariance (ANCOVA) were used to compare between the four risk-groups (while controlling for baseline) in a pairwise manner.

### 5.4.2 Missing data

Missing data can refer to either missing items or missing questionnaires (or part of questionnaires). Missing data can be dealt with differently depending on the situation. Due to technical error during the collection of data, 63 men were not given the opportunity to respond to the worry questionnaire at baseline in S3QOL and the subscales (A) and (B) in the Attitudes and health behavior questionnaire were incomplete at follow-up. In **Paper III** and **IV**, those missing men in the worry questionnaire were removed from the analysis and in **paper IV**, the analysis of the subscales (A) and (B) of the Attitudes and health behavior questionnaire had to be omitted altogether.

# 6 ETHICAL CONSIDERATIONS

All studies included in the thesis have received ethical approval, including amendments, from the Regional Ethical Review Board in Stockholm. The SARA study was approved in 2011 (ref 2011/630-31/4). The STHLM3 study was approved in 2012 (ref 2012/572-31/1). The S3QOL study was conducted following an addition to the application for STHLM3. This addition was approved May 27th 2013.

## 6.1 PAPER I

Population based selection of individuals for invitation to respond to questionnaires includes the risk that recipients who are affected by cancer may be affected by worry as they are reminded of cancer and maybe screening/testing. They may also suspect that they have been selected based on their cancer experience. None of those invited has, however, contacted us concerning this problem.

## 6.2 PAPER II / STHLM3

Data for this paper was collected during the STHLM3-pilot study. This particular paper is a methodological paper that investigated the relative influence of different survey design factors on ensuing participation in STHLM3 trial. The reason those survey design aspects were evaluated was because concerns were raised over the optimal mailing procedures, including the use of pre-notification, length of invitation letters and questionnaires for the main study. Participants did not know that these survey design factors were the subject of a randomised controlled trial. Being allocated to different survey design arms is not research that involves sensitive information or biological material, and thus by law does not require ethical approval (83). The ethical application for STHLM3 pertains to the sensitive information and collection of biological material conveyed in the STHLM3 questionnaire and the blood provided within the frame of STHLM3. However, this study was important from an ethical aspect in the sense that STHLM3 and its ensuing PCT were going to involve a large sample of the population. Ergo, there was an ethical impetus to optimize participation. The results of **Paper II** were used in the STHLM3 trial, resulting in improvement of the participation rate.

## 6.3 PAPER III AND IV / S3QOL

An ethical aspect that needs to be discussed is the invitation at the first time point. When invited in January 2014, the men did not know about the impeding invitation to STHLM3 in April of the same year. In other words, they did not know of the longitudinal aspect of the S3QOL study. One could argue that it is not ethical to keep information from participants. But in weighing the pros versus the cons, we reasoned that achieving a "true" baseline measurement, i.e. not contaminated by the knowledge of the upcoming PCT/STHLM3, weighed heavier than disclosing how/why they had been chosen. Having that knowledge could have undermined the longitudinal study as a whole. Moreover, telling them about the upcoming PCT could have influenced their participation in the sense that they could have felt coerced to participate at the first time point in order to get to participate to STHLM3 later on, which was not the case. It would also probably have affected the results, as we were interested in investigating factors for participation outside the prospect of invitation to testing. The men could choose to ignore to participate or withdraw from the study at any point. Finally, although belonging to the S3QOL study sample meant being invited to respond to a questionnaire at three time points in a year, we lowered the eventual information burden or saturation the participants might feel by not sending reminders.

# 7 RESULTS

## 7.1 PARTICIPANTS

- Study I: Of the 10.000 individuals invited, 5049 were men. Among those, 1384 men (27%) responded to our web-survey. Among the non-respondents, 75% said in the interview that they wanted to know their risk. Respondents and non-respondents were not significantly different in age and sex. The most common reason for non-participation stated in the interviews was 'lack of time'.
- Study II: Out of the 28.134 men included in Study II, a total of 9.543 men (34%) participated to STHLM3. Among them, 7.302 men provided blood for PCT *and* responded to the STHLM3 questionnaire; and 1.744 men only did PCT,
- Study III: Out of the 10.000 men invited to S3QOL, 1.980 men (20%) responded to the S3QOL survey three months before invitation to STHLM3. Among them, 70% participated in the ensuing PCT within STHLM3, and 30% did not participate in STHLM3.
- Study IV: Among the 10.000 men invited to S3QOL, a total of 994 men performed PCT and responded to the S3QOL survey at baseline and follow-up and were thus included in the analyses. Among them, 421 men were identified as 'Low risk', 421 men as 'Intermediate risk' and 152 men as 'High risk' (93 men with a benign biopsy result and 59 men with a confirmed PCa diagnosis).

## 7.2 LEVEL OF INTEREST TO INDIVIDUALIZED PROSTATE CANCER TESTING

The level of interest to individualized PCT and acceptability of risk-stratified PCa screening was assessed in **Paper I**. A vast majority of the men (95%) stated wanting to know their PCa risk with 73% responding "Absolutely" and 22% "Maybe". The major reasons for wanting to know one's risk were to avoid worrying (89%), to get a realistic view of the future (83%) and to get rid of uncertainty (78%).

A total of 69% stated that they would like to participate in an organized prostate cancer screening. If identified with a high risk, they stated that they would agree to undergo screening more often than average. When asked "If identified as having a low risk, would you agree to undergo screening less often than average?", a majority of the men were still

positively inclined in doing so, but the level of certainty dropped. Older age predicted being more certain, whereas higher education was associated with less certainty.

Moreover, in order to assess their PCa risk, 62% of the men responded being comfortable in conveying personal information and 71% comfortable in conveying genetic information.

Finally, the preferred mode of communication of the risk was via consultation with a GP but almost 60% of the men were accepting communication via mail.

## 7.3 PREDICTORS OF PARTICIPATION TO INDIVIDUALIZED PROSTATE CANCER TESTING

Through **Paper II** and **III** we researched factors upstream of PCT that could increase or predict ensuing PCT uptake.

**Paper II** investigated methodological aspects that might affect subsequent participation to PCT and revealed that use of a pre-notification increased PCT uptake, both among men who only provided blood for PCT ($p=0.002$) and among men who provided blood for PCT and completed the STHLM3 questionnaire ($p=0.0007$).

**Paper III** investigated psycho-social factors in relation to PCT participation by comparing baseline measurements before invitation of men who subsequently declined participation to PCT to men who participated. The following results were found:

- A higher proportion of participants reported worry to some degree ($p=0.02$)
- A tendency among participants to perceive their risk of getting PCa as slighlty higher than decliners ($p\leq0.05$)
- A tendency among participants to consider their likelihood of developing PCa in the next five years as slightly higher than decliners ($p=0.003$)
- Levels of knowledge were low in both groups since less than 50% responded correctly to five of the six knowledge items. However, Decliners responded “Do not know” more often.
- Participants indicated greater benefits of prostate testing ($p=0.0005$), less barriers to PCT ($p<0.0001$) and a higher desire for better general health ($p=0.03$)

- Participants presented a better global health status ($p<0.0001$)

## 7.4 PSYCHOSOCIAL EFFECTS OF PARTICIPATION TO INDIVIDUALIZED PROSTATE CANCER TESTING

In **Paper IV**, the men's psycho-social factors downstream of PCT were compared at follow-up to their answers at baseline to investigate possible effects of PCT participation over time. When compared to baseline, Low-risk individuals and Intermediate-risk individuals reported reduced worry levels at follow-up. Additionally, high-risk individuals did not report increased worry levels at follow-up. High-risk individuals, who had had a negative biopsy, reported a reduction in their perceived likelihood of developing cancer in the next five years, whereas high-risk individuals who had been diagnosed with PCa reported an increase in PCa worry affecting their daily life.

A vast majority of the respondents answered incorrectly at the questionnaire on PCa knowledge, whether at baseline or at follow-up, reflecting a low level of knowledge across the groups. Group comparisons between the different risk-levels suggested that high-risk men had learned more over time than low-risk and intermediate-risk men.

Both the Low risk group and the Intermediate risk group scored statistically significantly lower on "External influences" and "General Health" at follow-up compared to baseline. In the High-risk group and in the PCa diagnosis group, "Barriers" increased over time. The High-risk group and the PCa diagnosis group scored statistically significantly higher on "Barriers to screening" than the Low risk group. This difference ($p<0.001$) was also found when comparing the Intermediate risk group to the High-risk group and the PCa diagnosis group.

No statistically significant changes between baseline and follow-up were found for HRQoL in any of the groups, with one exception. Emotional functioning improved over time in the Intermediate-risk group.

# 8 DISCUSSION

There are still many aspects that need studying before PCa joins the rank of screening programs offered to the general public. However, this thesis and the paper it encompasses, sheds light on men's interest and acceptability towards a risk-based PCa screening program. and adds knowledge concerning psychosocial characteristics surrounding individualized PCT.

One of the criteria for a screening program to be adopted is that "The test should be acceptable to the population"(41). Although hampered by a low-response rate, the results of **Paper I** suggests that there is a public interest in and acceptability of establishing risk-stratified screening programs. This goes along the line of previous studies that found a similar high interest in genetic testing and personalized screening (84-86). There seems to be, however, a discordance between claimed interest and actual uptake. A total of 73% of the men who responded to Study I stated that they would like to know their PCa risk, whereas approximately 40% of the STHLM3 study sample ended up participating and performing a risk-based PCT. For example, the European Guidelines for Quality Assurance in Breast Cancer Screening recommend an uptake of at least 70%. However, only half of 26 European breast cancer screening programs achieve that percentage (87). Some of the reasons stated for not attending a routine breast screening are "feeling embarrassed", "having a lack of breast cancer symptoms", and "forgetting to go to the appointment" (88). A colorectal cancer screening study found that personalized cancer risk information could either increase or decrease an individual's interest in colorectal cancer screening, depending on prior screening history, estimated cancer risk and baseline screening interest (89).

Although there is an interest to participate in prostate cancer testing and an acceptability for an individualized screening program, there seems to be, however, more hesitancy for being screened less often if identified as having a low risk of PCa than for being screened more often if identified with a high risk. More research is needed to see whether men would accept the recommendation of not needing to be screened again if having a low risk. More research is also needed to see if that hesitancy would affect PCT uptake.

The results presented in this thesis increase our knowledge around factors that affect men's participation in risk-based PCT. As presented in **Paper II**, the use of a pre-notification card increased participation to the web-survey, but more importantly, it also increased participation in PCT. Moreover, as discussed in **Paper III**, when PCT participants were compared to PCT decliners, 70% of our respondents ended up participating in the ensuing PCT (compared to the 40% observed in STHLM3). This could be due to selection bias, but we cannot rule out that the baseline questionnaire in itself triggered an interest in PCT (a little bit like a pre-notification) and increased participation to PCT. Thus, responding to the questionnaire might have reinforced PCT participation. However, more research is needed to understand what aspect of the pre-notification and possibly questionnaire might affect PCT uptake.

As shown previously in several studies, men undergoing PSA testing do not show any significant increase in anxiety, even with an abnormal PSA result (55, 56, 59). Similarly, **Paper IV**, did not observe higher worry levels among men with an abnormal PSA result. Interestingly, **Paper IV** showed a decrease in worry level among men with normal PSA results. These results reinforce and justify the notion that the mental harm of PCa screening is not source of major concern.

When deciding upon whether to offer PCT or not to the general population, The Board of Health and Welfare (Socialstyrelsen) investigates, among other, whether the test method is accepted by the population (90). It has been shown that men who find out that they have a "normal" PSA-test find that reassuring (91). Our results in **Paper IV** showed that men who find out that they have a low or intermediate risk of developing PCa reported decreased worry levels. Moreover, "integrate education" and "ensure informed choice" are two screening criteria that need to be met for a screening to be adopted. The results in **Paper IV** shed light on the need for more education around PCT.

The present findings concerning PCT participation and its lack of effect on HRQoL concur with those of other international studies (55, 60, 61) . Similarly to Hewitson *et al. (92)* who claimed that it was only with the development of a breast cancer screening-specific instrument (the Psychological Consequences Questionnaire (93)) that subtle measures of cognitive and emotional responses to screening could finally be detected. (92), Brindle et al.

suggests that the used instruments may not adequately measure the psychological impact associated with PCT participation, explaining the failure to detect possible psychological effects of screening (56).

Because the response rates in our surveys were low, we are faced with the risk that respondents differ systematically from non-respondents. Indeed, the participants in our study probably had an initial interest in the subject to want to log-in and respond to our web-surveys. This creates a participation bias (or non-response bias). It is a phenomenon in which the results become non-representative because the participants are systematically different from the target population, and may bias the results. Epidemiological and psychological research often involves questionnaires or web-surveys, and it has become more and more difficult to achieve high response rates when studying the general population. (94, 95). However, although not perfect, our non-respondent analysis for **Paper I** showed that a majority of the non-respondents stated wanting to know their cancer risk and that lack of time had been a common reason behind not answering.

For a screening program to be worthwhile, the uptake within the concerned population needs to be high. Our results are giving indications as to which men would seek PCT and which men would decline PCT in terms of psycho-social factors. This information will help inform health policy makers in order to increase participation in risk-based PCT. In line with other studies that showed that PCa knowledge is a predictor of participation in PCa screening, our results reinforce the need for more education in relation to PCT (96, 97). Especially since the decision to undergo PCT, whether PSA-based or risk-based, relies largely on an educated and informed decision.

# 9 CONCLUSIONS

The results presented in this thesis add to the body of evidence regarding participation in individualized prostate cancer testing from a psycho-social standpoint. There is an interest to participate in prostate cancer testing, and there is an acceptability for an individualized screening program. There seems to be, however, more hesitancy behind the idea of being screened less often if identified as having a low risk of PCa than behind the idea of being screened more often if identified with a high risk. However, according to **Paper IV**, from a worry perspective, the men who were recommended to be screened less often, were the ones who gained the most from performing PCT since their worry levels decreased after performing risk-based PCT. More importantly, being identified as having a high risk for PCa did not induce heightened worry levels over time.

Men identified as having a high risk perceived more barriers concerning PCT at follow-up. Moreover, men identified as having a low or intermediate risk reported being less affected at follow-up by external influences and by aspects concerning health. Finally, only two differences were observed in terms of HRQoL. Men with intermediate risk reported increased emotional functioning over time and, surprisingly, men who were diagnosed with PCa presented a tendency to lower levels of pain over time, especially when compared to the low risk group. Otherwise, no differences were observed in terms of change of quality of life by undergoing PCT.

When compared to men who declined participation to PCT, men who participated in PCT reported slightly more worry as well as a heightened perceived vulnerability to PCa. Moreover, PCT participants perceived more benefits and less barriers from PCT participation than PCT decliners. Additionally, PCT decliners reported a lower global health status, lower emotional functioning and higher levels of fatigue compared to PCT participants.

As for PCa knowledge, no differences were observed between PCT participants and PCT decliners. The level of knowledge was low overall. Interestingly, where participants and decliners differed was in the certitude of the knowledge, i.e. decliners more often responded "Do not know". More research is needed to understand how this knowledge (or lack thereof)

affects PCT uptake. Our results suggest that undergoing PCT did not increase their level of knowledge over time, unless identified as having a high risk. Information about PCa and the pros and cons with PCa-testing have to be improved in the public in order for men to take an informed consent to participate.

# 10 POPULÄRVETENSKAPLIG SAMMANFATTNING

## 10.1 BAKGRUND

Prostatacancer (PCa) är den vanligaste cancerformen hos män i Sverige och utgör en tredjedel av cancer hos män. År 2016 fick 10 474 män diagnosen PCa. Socialstyrelsen rekommenderar inte screening för PCa med enbart prostataspecifikt antigen (PSA-prov) (43). Nackdelen med screening med enbart PSA-prov är att många män diagnosticeras med PCa trots att sjukdomen aldrig riskerar att utvecklas till en allvarlig sjukdom. Detta innebär att många män utsätts för biopsi och ev. komplikationer i onödan, samt får leva med en PCa diagnos och de psykosociala konsekvenser som medföljer. Det anses därför att nyttan med PSA-screening inte överväger de negativa effekterna.

Flera tester som kan komplettera PSA-provet har utvecklats under senare år vilket ger möjlighet att minska överdiagnostik och överbehandling. En metod som utvecklats är STHLM3-modellen. Utöver PSA ingår olika markörer samt genetisk information för att beräkna den individuella risken för PCa. STHLM3-modellen har visats vara bättre när det gäller att identifiera högrisk PCa och samtidigt minska behovet av biopsi. Baserat på en riskprofil (låg, normal eller hög) kan individanpassad screening erbjudas. I dagsläget finns det dock ej mycket kunskap kring hur en sådan individanpassad PCa test skulle påverka männens hälsorelaterade livskvalitet (HRQoL), deras attityder till deltagande i screening och PCa-testning (PCT), samt deras kunskaper om PCa.

Det övergripande syftet med denna avhandling var att undersöka ovanstående aspekter av risk-baserad PCT.

**Artikel I**: att utforska intresset för och acceptans i befolkningen av individanpassad PCT och mammografiscreening.

**Artikel II**: att undersöka faktorer vid inbjudan till PCT såsom påannonsering, inbjudningsbrev, frågeformulär och påminnelse för att optimera deltagande i PCT.

**Artikel III**: att undersöka sambandet mellan deltagande i PCT och oro, kunskap, attityder kring PCT samt HRQoL tre månader före inbjudan till PCT.

**Artikel IV**: att undersöka skillnader mellan de olika riskgrupperna (låg, normal, hög) fem månader efter PCT rörande oro, kunskap om PCa, attityder kring PCT och HRQoL, samt undersöka om dessa faktorer ändras över tid i de olika riskgrupperna.

## 10.2 METODER

Data för **Artikel I**, **III** och **IV** insamlades med frågeformulär. I **Artikel II** randomiserade männen till olika former av inbjudningsfaktorer till PCT. Frågeformulären som användes i **Artikel I** utvecklades av en expertpanel, med frågor om befolkningens intresse av att veta sin individuella cancerrisk samt i vilken utsträckning de skulle acceptera att delta i en risk-baserat screeningprogram. Frågeformulären i **Artikel III** och **IV** utgörs av frågor som använts i tidigare forskningsstudier och består av fyra formulär som mäter männens oro, kunskap, attityder gentemot PCT samt HRQoL.

I **Artikel I** inbjöds 10 000 personer mellan 20–74 år från Sveriges befolkning, med en svarsfrekvens på 28%. Svaren jämfördes mellan kvinnor och män, åldersgrupper samt utbildningsnivå.

**Artikel II** baserades på STHLM3:s pilot-studie, vilken innefattade 28 134 män randomiserade till sex olika inbjudningsfaktorer (påannonsering eller ej, kort eller långt inbjudningsbrev, kort eller långt frågeformulär och påminnelse eller ej) för att undersöka dessa faktorers påverkan på deltagande i PCT. Cirka 34% av de inbjudna deltog i påföljande PCT.

I **Artikel III** och **IV** inbjöds ett urval av 10 000 män som ingick i STHLM3-projektet till att svara på ett webbaserat frågeformulär vid tre tidpunkter: tre månader innan inbjudan till deltagande i STHLM3, i samband med deltagande i STHLM3 samt fem månader senare. Cirka 20% svarade vid den första tidpunkten medan cirka 10% svarade vid både det första och den sista tidpunkten.

## 10.3 RESULTAT

**Artikel I** rapporterade att majoriteten av både män och kvinnor var mycket intresserade av att känna till sin individuella prostata- respektive bröstcancerrisk. Män verkade en aning mer övertygade än kvinnor, men viljan var hög hos båda kön. Majoriteten ville screenas oftare om de skulle ha hög risk för PCa, men färre var intresserade av att screenas mer sällan än genomsnittet om de hade låg risk för PCa.

**Artikel II** visade att användandet av påannonsering samt påminnelse ökade deltagandet i PCT. Denna metod användes senare i inbjudningarna till STHLM3 och deltagandet ökade i jämförelse med pilotstudien där inbjudningsfaktorerna testades.

**Artikel III** visade att de som deltog i PCT skattade mer oro kring PCa samt en högre känsla av sårbarhet än män som ej deltog i PCT. Dessutom hade de som avböjde deltagande i PCT en något lägre HRQoL. Båda grupperna visade låg kunskapsnivå gällande PCa överlag.

**Artikel IV** rapporterade få skillnader gällande HRQoL över tid oavsett riskgrupp. Männen i högriskgruppen visade ingen ökning i oro över tid, men en minskning i orosnivån noterades över tid hos män som tillhörde låg- eller normalriskgrupperna. Även här noterades en låg kunskapsnivå gällande PCa överlag även om högriskgruppen visade en förbättring över tid.

## 10.4 SLUTSATS

Många människor är intresserade av att få information om sin individuella bröst- och protatacancerrisk, vilket är en förutsättning för riskbaserad screening. Inbjudningar till PCT kan optimeras genom påannonsering och påminnelse. Kunskaperna om PCa bland män i befolkningen är låg. Denna kunskapsnivå behöver förbättras för att män ska kunna fatta ett informerat beslut om de inbjuds att delta i PCT. Detta är viktigt om PCa screening skall införas. Att deltagande i PCa-screening leder till negativa psykosociala konsekvenser har varit ett av huvudargumenten för att inte införa screening. Föreliggande studie stöder inte detta antagande. Risk-baserad PCT tycktes inte ha någon negativ påverkan på männens välmående, oavsett riskgrupp

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