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Quality of life aspects of being diagnosed and living with prostate cancer

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Abstract
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Prostate cancer is largely a heterogenous disease, ranging from almost harmless to highly aggressive. Most men are diagnosed with favorable-risk disease with a long life expectancy even without treatment. The risk of overdiagnosing and overtreating these men is substantial, with reduced quality of life as a result. In this thesis, we study the diagnostics of, and the quality of life for men with prostate cancer.

In paper I, we studied satisfaction with care among men with low-risk prostate cancer in a nationwide, population-based setting and found a high overall satisfaction with care. Information and participation in decision-making were of great importance for satisfaction. However, men on active surveillance reported lower overall satisfaction with care, suggesting that they need more information and to be more participatory in their care.

In paper II, we investigated choice and adherence to active surveillance and found that a doctor's recommendation was the most important factor for choosing active surveillance as the primary treatment strategy. A rising PSA was the most common cause for diverting from active surveillance to curative treatment, even though PSA alone is a poor marker for disease progression.

In paper III, we explored lifestyle changes after a prostate cancer diagnosis and a possible association between lifestyle changes and quality of life. We found that a considerable proportion of men change their lifestyle after a prostate cancer diagnosis and that a positive lifestyle change was associated with a higher quality of life. However, men with poorer functional outcomes after treatment were less likely to make lifestyle changes, suggesting that these men need better support and rehabilitation.

In paper IV, we used a new simulation model to evaluate the benefit and harm of the increased PSA-driven diagnostic activity that has occurred over the last 30 years. We found that the increased diagnostic activity has resulted in a modest decrease in prostate cancer specific mortality but at the cost of substantial overdiagnosis and overtreatment.

To conclude, this thesis provides information on factors to improve satisfaction with care, increase adherence to active surveillance, and to engage in positive lifestyle changes, possibly contributing to a higher quality of life.

Keywords: Prostate cancer, Oncology, Active surveillance, Quality of life, Survivorship, Satisfaction, Choice, Adherence, Life-style change, PSA

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Till Filippa, Agnes och Alvar

List of Papers

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

I Bergengren, O., Garmo, H., Bratt, O., Holmberg, L., Johansson, E., Bill-Axelson, A. (2018) Satisfaction with Care Among Men with Localised Prostate Cancer: A Nationwide Population-based Study. *Eur Urol Oncol.* 2018;1(1):37-45

II Bergengren, O., Garmo, H., Bratt, O., Holmberg, L., Johansson, E., Bill-Axelson, A. (2019) Determinants for choosing and adhering to active surveillance for localised prostate cancer: a nationwide population-based study. *BMJ Open.* 2019;9(12): e033944

III Bergengren, O., Enblad, AP., Garmo, H., Bratt, O., Holmberg, L., Johansson, E., Bill-Axelson, A. (2020) Changes in lifestyle among prostate cancer survivors: A nationwide population-based study. *Psychooncology*. 2020 Aug 10;29(10):1713–9

IV Bergengren, O., Westerberg, M., Holmberg, L., Stattin, P., Bill-Axelson, A., Garmo, H. (2020) Benefit and harm of prostate specific antigen driven diagnostic activity, a 20-year nationwide population-based evaluation. *In Manuscript*

Contents

Abbreviations

AS	Active Surveillance
CCI	Charlson Comorbidity Index
DAG	Directed Acyclic Graphs
DRI	Digital Rectal Examination
EPIC-26	Expanded Prostate Cancer Index Composite-26
GS	Gleason score
ISUP	International Society of Urological Pathology
MRI	Magnetic Resonance Imaging
NPCR	National Prostate Cancer Register of Sweden
PCa	Prostate Cancer
PCBaSe	Prostate Cancer data Base Sweden
PRISM-PC	Proxy-based Risk-stratified Incidence Simulation Model - Prostate Cancer
PSA	Prostate-specific antigen
QoL	Quality of Life
RP	Radical Prostatectomy
RT	Radiotherapy
TNM	Tumor, Node and Metastasis
T-stage	Tumour stage

Introduction

This thesis, comprising four papers, focuses on the diagnostics of prostate cancer as well as the quality of life aspects of being diagnosed and living with prostate cancer. The first paper describes satisfaction with care among men with localized prostate cancer and identifies factors to increase satisfaction with care. The second paper describes choice and adherence to active surveillance for prostate cancer and identifies factors to increase the implementation of active surveillance. The third paper studies lifestyle changes after a prostate cancer diagnosis, identifies barriers to lifestyle change, and examines the relationship between lifestyle changes and quality of life. The fourth paper evaluates the benefits and harms of the PSA driven diagnostic activity that has increased over the past 20 years.

Background

Introduction and rationale behind the study

The availability of prostate-specific antigen (PSA) testing from the mid to late 1980s led to a rapid increase in the incidence of prostate cancer.[1] In Sweden, over 50% of all men aged 55 to 69 years have undergone PSA-testing at least once, in the absence of a screening program.[2] Prostate cancer is now one of the most common cancers among men worldwide and the most common cancer amongst men in Sweden.[1]

However, mortality rates do not follow those of incidence.[1] A large proportion of these men are diagnosed as having a low-risk disease, with a low-risk of metastasis and a very low-risk of cancer specific death.[3] In a long-term follow-up of a large cohort of men with favorable-risk prostate cancer, the likelihood of dying from other causes was about nine times greater than the risk of dying from prostate cancer; the prostate cancer specific mortality was only about 1.5%.[4]

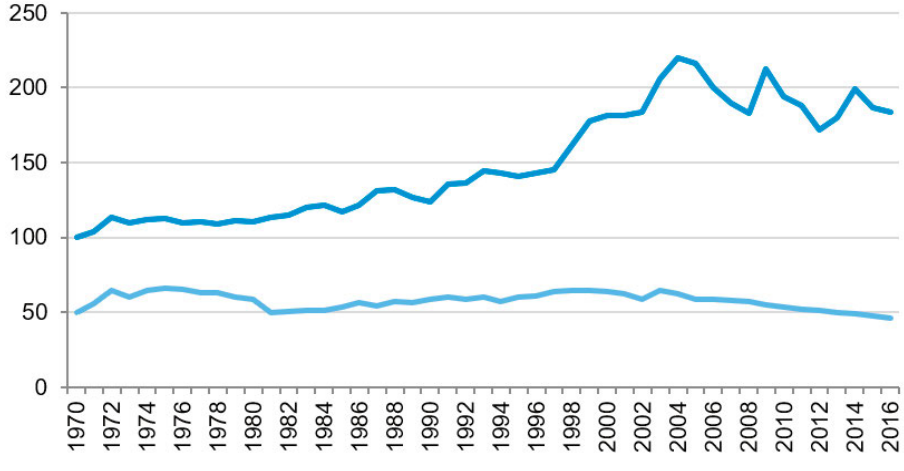

Figure 1. Age-standardized incidence (dark blue) and mortality (light blue) per 100,000 Swedish men. Source: National Guidelines for prostate cancer, www.cancercentrum.se

This increase in low-risk cases due to the increased PSA driven diagnostic activity leads to problems with overdiagnosis and subsequently overtreatment.

A large number of men have received and are still receiving unnecessary treatment (radical prostatectomy or radiotherapy) for low-risk disease, which results in unnecessary side effects such as erectile dysfunction, urinary leakage, and bowel problems from radiation.[5]

Active surveillance with selective delayed curative treatment was introduced in the late 1990s as an effort to reduce the overtreatment of low-risk disease.[6,7] It has emerged as the primary strategy for these men, although it has taken a long time for both patients and caregivers to accept.[8]

Active surveillance does not come without issues, as living with an untreated cancer might result in decreased quality of life due to anxiety. Previous studies on quality of life among men under active surveillance, however, have shown only modest effects on mental health and quality of life.[9-14] Further, this treatment strategy places high demands on care givers to be careful in selecting appropriate cases for active surveillance, to uphold the trust of these men during the long follow-up and to effectively identify disease progression during the course of surveillance. Several studies have shown the long-term safety of this strategy, and new modes of detection and follow-up such as MRI (magnetic resonance imaging) are emerging.[15]

Epidemiology

Prostate cancer is the second most common cancer among men worldwide and the most common cancer in over half of all countries.[1] It is the fifth leading cause of cancer specific death amongst men worldwide.[1]

From the mid to late 1980s, there was a rapid increase in incidence, starting in the United States and then in greater Europe, Australia, and Canada. In recent years, the incidence has declined in these countries, partly because the pool of prevalent cases has diminished. However, the incidence rates are still rising in e.g., Brazil and Thailand, where PSA-testing became more widely used later.[1]

If we look at Sweden, we can clearly see the same pattern as described above. There was a rapid increase during the late 1990s, mostly because of the increasing use of PSA-testing but also the possibility for biopsies, guided by ultrasound, better pathology, and an older male population. Although prostate cancer is still the most common cause of cancer specific death among Swedish men, the cancer specific mortality has gone down. This might be because of earlier detection and improvement in disease management.[16]

Diagnostics

The diagnostics for prostate cancer pose some of the biggest challenges regarding the management of the disease. As prostate cancer is such a heterogenous disease, ranging from almost harmless to highly aggressive, the risk of over diagnosing low-risk disease whilst under-diagnosing and subsequently under-treating high-risk disease is imminent.

Suspicion of prostate cancer traditionally arises after an elevated PSA is detected and/or after a pathological digital rectal examination (DRE). However, PSA is a blunt instrument with many sources of error such as urinary tract infections and benign prostate hyperplasia, resulting in false-positive results. Further, extensive PSA-testing has mainly shown to increase low- and intermediate risk disease, resulting in overtreatment with only modest effects on survival.[17,18] If there is a suspicion of prostate cancer, systematic biopsies of the prostate are performed for diagnosis, although transrectal ultrasound-guided biopsies have poor accuracy.[19]

In recent years, the use of MRI in the diagnostics of prostate cancer has been rapidly increasing. More and more clinical data support the use of MRI as a diagnostic tool to mitigate the issues of PSA-testing. In a recent review on the effectiveness of MRI in the diagnostics of prostate cancer, the authors found that the use of MRI reduced the number of low-risk cancers, whilst finding more high-risk and advanced disease. They concluded that MRI should be considered as a standard of care for the diagnostics of prostate cancer. However, they also pointed out that several challenges remain regarding the implementation of MRI such as the quality of execution, the reporting of the findings as well as cost-effectiveness.[20]

MRI-guided biopsies is now an option.[21] This approach is less invasive, leads to fewer biopsy's taken,[22] and subsequently reduces the number of biopsy-related adverse effects during the investigation of prostate cancer.

Staging and risk-groups

Here follows a brief summary of staging and risk groups for prostate cancer for a better understanding of the articles.

Newly diagnosed prostate cancer is classified according to the TNM-system, standardized by IUCC, which was revised in 2017. The T-stage ranges from T0–T4 and represents the growth and local spread; the N-stage ranges from N0–N1 and represents metastasis to the lymph nodes; and finally, the M-stage ranges from M0–M1 and represents distant metastasis.

PSA is an enzyme produced in the prostate, important for propagation. PSA is measured in the blood samples during the investigation and follow-up of prostate cancer.

Tissue from biopsies or surgery are analyzed microscopically by a pathologist using the Gleason system, where histological patterns are evaluated and graded from 2 to 5 (although GS 2 is rarely used in this context). A higher grade equals a more aggressive cancer. The most common pattern and the highest remaining score are noted (e.g., 3+4). These scores are then summarized, and the tumor is graded from Gleason grade 6 to 10. The grading system is standardized by the International Society of Urological Pathology and was last revised in 2014. To stratify the Gleason sums into prognostically relevant groups, the ISUP-grading system was introduced in which the tumor was graded from 1 to 5 with 5 being the most aggressive.[23] The most notable difference was that Gleason group 7 was divided into ISUP-grade 2 (Gleason grade 3+4) and ISUP-grade 3 (4+3).

Prostate cancer without metastasis is divided into 4 risk-groups (very low, low, intermediate, and high) based on the T-stage, PSA, and the biopsy results.

Prostate cancer is a heterogenous disease with the mortality rates varying substantially between the risk groups. The prostate cancer specific mortality after 10 years among untreated men is 4.5% for low-risk disease, 13% for intermediate-risk, and 29% for high-risk disease.[24]

Treatments

Active surveillance

Active surveillance is a treatment strategy with selective delayed curative treatment when signs of tumor progression are present; today, it is the recommended treatment for very low-risk and low-risk prostate cancer.[21]

As described in the introduction, a large proportion of men with prostate cancer are diagnosed with low-risk disease with low malignant potential and a long life expectancy even without curative treatment.[4] Active surveillance therefore has emerged as the primary strategy for these men to reduce unnecessary treatment.

Sweden has come a long way regarding active surveillance, largely due to clear national guidelines that had listed active surveillance as the primary treatment strategy for low-risk prostate cancer already in 2007. Uptake on active surveillance in Sweden has increased over the last decade and reached 91% for very low-risk and 74% for low-risk disease in 2014.[2] Several studies have been conducted on the safety and efficiency of active surveillance. Among the largest is the randomized trial ProtecT, where 1,643 men with localized prostate cancer were randomized to either prostatectomy, radiotherapy, or active surveillance. At a median of 10 years follow-up, there was no difference in prostate cancer specific death.[25]

It is important to note that despite the introduction of active surveillance there is still considerable overtreatment and that the optimal strategy for

follow-up and triggers for treatment are not yet established. There are no randomized trials on when to initiate treatment why the Prostate cancer active surveillance trigger trial (SPCG-17-PCASTt) [26] has been initiated. In this trial, men who are eligible for active surveillance is randomized to either standard of care or to a follow-up with standardized triggers for treatment.

An obvious question that arises when reflecting on active surveillance is what it is like for these men to live with an untreated cancer. It is easy to think that levels of anxiety must be high, resulting in a low quality of life. However, several studies have been done on this matter over the years, and results show only modest effects on psychological well-being. For example, a systematic review by Carter et al. concluded that clinicians do not need to limit access to active surveillance, based on expectations of adverse impacts on psychological well-being.[14]

Another question that arises is if there is a risk of disease progression during active surveillance. Surveying an untreated cancer puts high demands on healthcare to be particularly careful in selecting patients and monitoring the disease for early detection of progression. A recently published article by Van Hemelrijk et al. investigated reasons for discontinuing active surveillance and found approximately 44% drop-out during a five-year period, mainly due to cancer progression.[27] However, this means that 56% of the men in this study remained on active surveillance, thus, avoided unnecessary treatment with associated side effects. Klotz et al. published long-term follow-up data on a large cohort of men managed by active surveillance in 2015 and concluded that active surveillance was safe and that after 15 years, only 1.5% had died of prostate cancer. This is consistent with the expected mortality among favorable-risk patients, managed with definitive treatment such as radical prostatectomy or radiotherapy.[4] In conclusion, active surveillance is a safe option, both physically and psychologically, for men with favorable-risk prostate cancer.

Curative treatment

As described above, the two main alternatives for treatment with curative intent is radical prostatectomy or radiotherapy. There has long been a debate on which option is superior. Several studies have been conducted on the matter; however, no significant difference has been found in disease specific mortality. Hamdy et al., for example, randomized 1,643 men to active surveillance, radical prostatectomy, or radiotherapy between 1999 and 2009 and found a low disease-specific mortality overall and no significant difference between the treatment groups.[25]

The method for the modern nerve-sparing prostatectomy was developed in the early 80s by Patrick Walsh[28] and is still, together with radiotherapy, the recommended treatment for patients with intermediate and high-risk disease. During a radical prostatectomy, the prostate is removed together with the seminal vesicles, either using open surgery or a laparoscopic approach, often

robotically assisted. The main issues with this approach, besides all the inherent risks posed by major surgery, are the relatively common side effects such as erectile dysfunction and urinary leakage. In a relatively recent study on men with localized prostate cancer, who underwent robotic radical prostatectomy by relatively experienced surgeons, 74% experienced erectile dysfunction and 16% suffered from incontinence 2 years post-surgery.[29] There is no consensus on how to report urinary incontinence or what classifies as urinary incontinence which complicates comparisons between studies.

Radiotherapy is usually given as external radiation, divided into smaller doses called fractions (together with neoadjuvant and adjuvant androgen deprivation therapy in high-risk tumors). Radiotherapy can also be given in close proximity to the tumor (brachytherapy), with or without the addition of external radiation. Similar to the radical prostatectomy, a common side effect is erectile dysfunction; however, instead of risking urinary leakage, there is a risk of bowel symptoms due to the close proximity to the rectum. In the previously described, large randomized trial, ProtecT, the patient reported functional outcomes were analyzed at 6 months, 12 months, and then annually thereafter. Radiotherapy had better functional outcomes, in terms of sexual function and urinary incontinence but a higher rate of bowel-related symptoms and urgency to urinate.[30]

As described above, the major difference between these two treatment options are the side effects, and it is often up to the patient to choose his preferred method. However, there are certain situations where one option is better than the other. Men with severe lower urinary tract symptoms, for example, are not well suited for radiotherapy as these symptoms will probably worsen, resulting in a low quality of life. Likewise, men with previous major surgery to the lower abdomen/pelvic region might not be suitable for surgery due to a higher risk of complications.

It is important to note that the key challenge is not choosing the type of treatment, but carefully selecting men for curative treatment or for surveillance.

Options for men not eligible for curative treatment

As prostate cancer is a disease with long life expectancy, men with severe comorbidity are not always eligible for curative treatment, even in the event of disease progression. The recommended strategy for these men is watchful waiting, where they are closely monitored and given adequate palliative treatment when necessary (described below). In a highly recognized trial on prostate cancer, the SPCG-4, men were randomized to either radical prostatectomy or observation. At a median follow-up of over 20 years, the mortality rate was lower in the group that received curative treatment; however, the number of men who needed to be treated to save one life was relatively high, and many men in the observation group did not require any palliative treatment.[31] The

main challenge regarding watchful waiting is timing; too early and men will live with the side effects from the palliative treatment for longer than necessary, too late and symptoms from tumor progression such as painful bone-metastasis might be worse than they would have been otherwise. Hormonal treatment does not come without sacrifice, as side effects are severe (anemia, fatigue, hot flushes, and loss in sexual function, increased fracture risk as well as a negative impact on body mass and insulin sensitivity).[32]

The management of men with advanced disease is focused on palliation; prolonging life, whilst minimizing and postponing side effects from the treatment. Advanced prostate cancer can in many cases be effectively suppressed for years.[33] There have been major gains in the treatment of advanced disease, with the introduction of new treatments into clinical practice. Traditionally, advanced disease was treated with androgen deprivation therapy and progression during hormonal treatment with the addition of secondary hormonal manipulation.[34]

Data from the last decade have changed how patients with metastatic disease are treated, as the addition of early chemotherapy and new androgen deprivation therapies such as abiraterone or enzalutamide has shown positive results on survival.[35-38] The introduction of these therapies has also shown promising results on quality of life with a slight benefit for the new androgen deprivation therapies over early chemotherapy.[39-41] Additionally, radiotherapy against the primary tumor and possibly against metastasis has emerged as a promising option for oligometastatic disease. One of the largest studies regarding advanced and metastatic disease, the STAMPEDE trial, has shown survival benefits for chemotherapy (Docetaxel) already at the start of hormonal treatment as well as a survival benefit for radiotherapy against the primary tumor in men with a low metastatic burden.[35,42] These are significant findings that may benefit and possibly provide some hope, for men with advanced disease.

Psychological and social aspects of prostate cancer

In this thesis, I studied the psychological aspects of prostate cancer. A cancer diagnosis is a life-changing event, both for the patient as well as for the family and close friends. It causes anxiety, stirs up emotions, and raises questions and concerns about the future. It is one of the most emotionally charged diseases, placing high demands on caregivers, in terms of professionalism and support.

Quality of life research has become more frequent over the past decades as researchers has acknowledged it´s importance. A quick PubMed search on ‘quality of life’ shows that the number of publications has increased exponentially from just under 2,000 publications in 1990, to almost 40,000 publications in 2019. Quality of life can be described as an individual’s overall satisfaction with life and is of the utmost importance for patients. It is not easy to

define or to measure as it reflects numerous aspects of life such as mental health, social aspects, and functional outcomes from treatment. Quality of life is usually assessed by questionnaires where specific answers are assigned points that are summarized in to one or more scores which is the measure of quality of life. An example that is commonly used among cancer patients is the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [43]. The questionnaire used in this thesis is described in detail on page 29, "Methodological considerations".

In a recently published review on depression and the risk of suicide among men with prostate cancer, Fervaha et al.[44] concluded that almost 1 in 6 men experienced clinical depression compared to the global prevalence of around 1 in 20.[45] This is a substantial difference, illustrating the difficulties and impact of a cancer diagnosis. The choice of treatment did not affect whether these men became depressed. However, as expected, men with hormonal treatment more often presented with clinical depression. In my population, around 1 in 10 men reported suffering from depression, which is lower than the proportion in the review, but still higher than the general population. It is worth noting that my population comprises men with low-risk disease, which could explain the differences between my results and the results in the review. Fervaha et al.'s review study also concluded that there was an increased risk of suicide among men with prostate cancer and that up to 30% of these men did not have a previous diagnosis of depression. One study in the review found a doubled risk of suicide over 10 years compared to the general population.[46]

It is evident that men who are diagnosed with prostate cancer suffer psychologically. It is of great importance that we as healthcare professionals do all that we can to help. Specifically, we need to be better at identifying symptoms of depression. We also need to be better at informing our patients, both about the disease, but also about the risks of psychological distress. An example that likely represents a lack of information is that almost 10% of men on active surveillance in my first paper believed that they would die from prostate cancer although the real long-term prostate cancer specific mortality among men with favorable-risk prostate cancer is around 1.5%.[4]

Another important aspect of the psychosocial effects of cancer is how it affects the family. A recent Japanese study on the risk of depression among spouses of cancer patients showed an increased risk of depression after the cancer diagnosis, which illustrates the impact of a cancer diagnosis within the family.[47] Interestingly and counterintuitively, a recent French study on the risk of depression among older couples facing cancer showed that a higher level of anxiety in the cancer patient was associated with a decreased risk of depression in the spousal caregiver.[48]

Simulations models

A simulation model is basically a computer program which, based on known data (from e.g., national registries or previous trials), simulates new data which provides a useful tool in epidemiological research. For example, a recent paper by Getaneh et al. compared different screening strategies for prostate cancer by using simulated data on 230 different PSA-based screening strategies and found that the most optimum strategy would be to screen with 3-year intervals from age 55 to 64.[49] The main advantage here is being able to compare large datasets, where a clinical trial would be impossible. However, it is important to note that these are simulated data and therefore only provide an overview and should not be interpreted as exact data.

The two existing models, the MISCAN[50] and FHCRC,[51] have mainly been used to compare competing strategies for disease screening.

In this thesis, I use a new simulation model, the Proxy-based Risk-stratified Incidence Simulation Model - Prostate Cancer (PRISM-PC). What is new about the PRISM-PC-model is that it uses observed data from the Prostate Cancer Database Sweden (PCBaSe) and simulates real-life scenarios, rather than assumptions on the natural history of prostate cancer, based on a variety of selected data materials and clinical trials.

The PRISM-PC-model, in brief, works by first assessing the diagnostic activity for prostate cancer in a population; then, it simulates incidence and risk category; and finally, it simulates mortality in steps of one year at a time. In an additional step, it samples treatment trajectories from men in PCBaSe with similar cancer characteristics. The model is described in more detail in the methods section of paper IV.

Aims of the studies

Overall aim

The overall aim of this thesis was to get a better understanding of what it is like to be diagnosed and to live with prostate cancer, and to find factors that can be improved.

Paper I

Studies on overall satisfaction with care among men with prostate cancer are lacking. Therefore, our first study focused on different factors affecting overall satisfaction with care.

The aim of this paper was to describe the overall satisfaction with care among men with localized prostate cancer and to identify factors that affected their overall satisfaction with care.

Paper II

Uptake on active surveillance among men with low-risk disease has steadily increased over the past decade, but there is still a considerable proportion of men who receive immediate curative treatment although guidelines are clearly in favor of active surveillance.[2] Additionally, a considerable proportion of men on active surveillance diverge to curative treatment over time with no signs of disease progression.[52] Therefore, our second study focused on factors affecting choice and adherence to active surveillance.

Specifically, the aim of the second paper was to describe choice and adherence to active surveillance and to identify factors associated with choice and adherence.

Paper III

Lifestyle changes may improve quality of life and reduce the risks of both cancer recurrence and non-cancer mortality.[53-57] There are very few studies on lifestyle changes after a prostate cancer diagnosis in a population-based

setting. Therefore, our third article aimed to identify factors potentially associated with lifestyle change and determine whether there is an association between lifestyle changes and quality of life.

Paper IV

Paper IV differs from the previous papers in that it uses a different dataset and a different methodology.

In this paper, we use a new simulation model, the Proxy-based Risk-stratified Incidence Simulation Model - Prostate Cancer (PRISM-PC), which simulates the outcome, depending on different levels of diagnostic activity.

The aim was to evaluate the benefits and harm of the PSA driven diagnostic activity that has increased over the past 20–30 years, by comparing the number of men diagnosed with prostate cancer, treatments given, and prostate cancer specific death between real data (with the extensive, opportunistic diagnostic activity that has occurred) and a simulated scenario with a much more restrictive diagnostic activity.

Materials and methods

Data collection

Papers I to III all use the same dataset. Between February and October 2015, 1,720 men, registered in the National Prostate cancer registry of Sweden (NPCR), were invited to answer an extensive questionnaire. NPCR is a nationwide registry of prostate cancer and has a capture rate of > 96% compared with the national cancer registry, to which registration is mandatory by law.[58]

These men were all diagnosed in 2008 with localized prostate cancer, with a Gleason score of 6; prostate-specific antigen (PSA) < 10 ng/ml; clinical stage T1 or T2; and were treated with radical prostatectomy, radiotherapy, or managed with active surveillance. The reason for choosing men diagnosed in 2008 was so that we could obtain long-term data.

The questionnaire comprised a study-specific part and EPIC-26, which is a validated instrument to assess functional outcomes in prostate cancer patients.[59] The study-specific part was created after in-depth interviews with men living with prostate cancer and explored areas such as sociodemographic, smoking, alcohol habits, physical activity, concurrent diseases (Charlson Comorbidity Index[60]), psychiatric problems, mental symptoms, quality of life, lifestyle changes, experiences at the time of diagnosis and at follow-up, treatments, side effects from treatment, and satisfaction with care. Additional information from NPCR relating to age at diagnosis, PSA at diagnosis, T-stage, method of detection, and time from diagnosis to treatment were obtained.

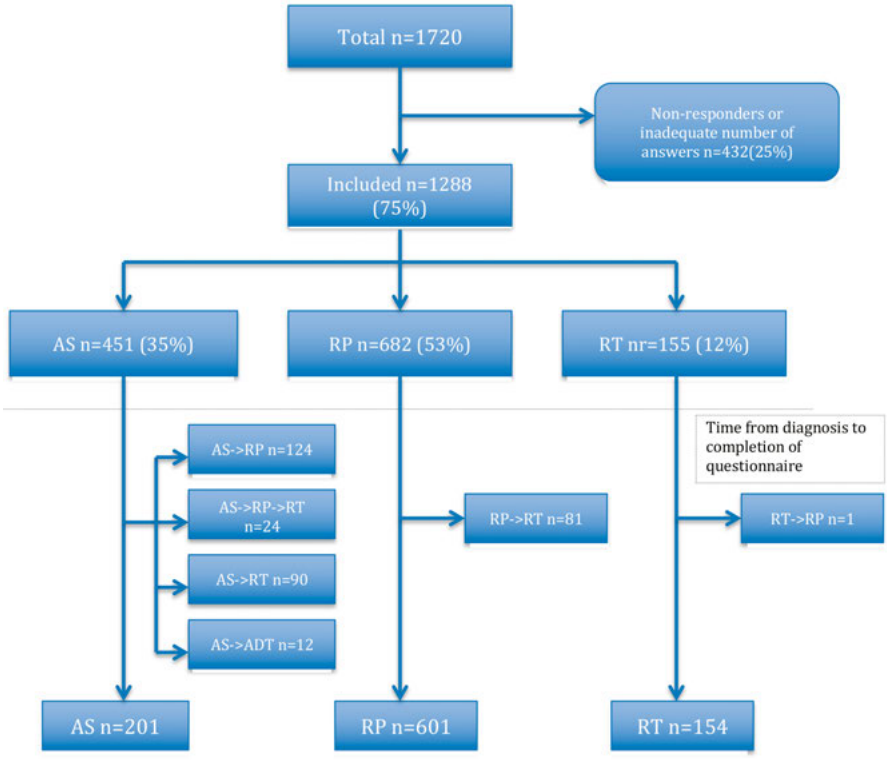

Figure 2. Flow-chart showing patients and treatments for papers I-III. AS = Active Surveillance; RP = Radical Prostatectomy; RT= Radiotherapy; ADT= Androgen Deprivation Therapy.

For paper IV, we used a different dataset comprising all Swedish men with a prostate cancer diagnosis from 1992 to 2016. The dataset includes demographics, risk category, treatments, and prostate cancer specific death. The dataset also comprised corresponding, simulated data on a scenario with a lower diagnostic activity.

Paper I

Study design

Paper I used the data described above. Specifically, the last question of the questionnaire, "Overall, how satisfied are you with the medical care you have received as a prostate cancer patient?" The men could grade this question from 1–7, where 7 was the highest possible response rate, "completely satisfied." Participants were then grouped according to their initial treatment: active surveillance, radical prostatectomy, or radiotherapy. Potential factors associated with satisfaction were analyzed.

The study design was not intended to compare satisfaction between treatments, as we know that there is a selection bias that we cannot account for. Instead, the aim was to assess the patients' overall satisfaction with care to find potential areas for improvement.

Statistical analysis

A drop-out analysis was performed to identify differences between responders and non-responders. We used multiple imputation to handle missing data. Ordinal logistic regression was used to analyze factors potentially associated with overall satisfaction with care. The analysis was adjusted for age, marital status, fatherhood, profession, education, Charlson comorbidity index, and psychiatric comorbidity. Data were presented as odds ratios, with 95% confidence intervals and show the probability to advance one step on the visual digital scale.

Paper II

Study design

In paper II, we used the same population-based data described above. Through the NPCR, we had access to information about the men's initial treatment and through the question "If you have received treatment for prostate cancer, which treatment(s) have you received up to date?", we had access to what treatment they had received upon completion of the questionnaire. Further, there were two direct questions on choice and adherence: "If you were on active surveillance for prostate cancer but later received treatment, or if you are still on active surveillance–which of the following alternative(s) influenced the decision?" and "Why was the active surveillance terminated and treatment initiated?" Using this information, together with information from our questionnaire and the NPCR, we could analyze choice and adherence both through the direct question and through a multivariate model.

Statistical analysis

The statistical analysis in paper II was performed similar to that in paper I. Again, missing data were handled through multiple imputations. Unlike in paper I, we performed a logistic regression analysis in paper II to find factors associated with choice and adherence to active surveillance. Directed acyclic graphs (DAGs) were used to identify confounding variables.[61,62] The analysis was adjusted for age, retirement, education, and CCI.

The direct questions on choice and adherence did not require any further statistical analysis.

Paper III

Study design

The study design in paper III was similar to that of papers I and II. We used the same dataset; however, this time we used the question "Has your prostate cancer diagnosis influenced your lifestyle in any way, and if so, in what areas?" The areas were specified as food, exercise, religion/philosophy, and social, where participants had the possibility to rate each of these as improved, unchanged, or worse. Quality of life was assessed by the question "During the last 4 weeks, what has your quality of life been like?," where the men had the possibility to grade this from 1 (No quality of life) to 7 (Best possible quality of life). We used DAGs to define factors potentially associated with lifestyle change.

Statistical analysis

The statistical analysis for paper III was performed similar to that in papers I and II, with the only difference being that for this paper, we used both logistic regression (to analyze factors potentially associated with lifestyle change) and ordinal logistic regression (to analyze a possible connection between positive lifestyle changes and quality of life).

Paper IV

Study design

The study design of paper IV differs from the three previous papers. The study aimed to evaluate the effects of the extensive, PSA-driven diagnostic activity that has taken place over the past 20 years. This was not a simple task, as there is no real, comparable data on alternative scenarios.

Consequently, we used a new simulation model, the PRISM-PC-model [63], to simulate a hypothetical dataset with a much more restrictive testing, namely the same diagnostic intensity as Sweden experienced in 1996, at the beginning of the PSA-era.

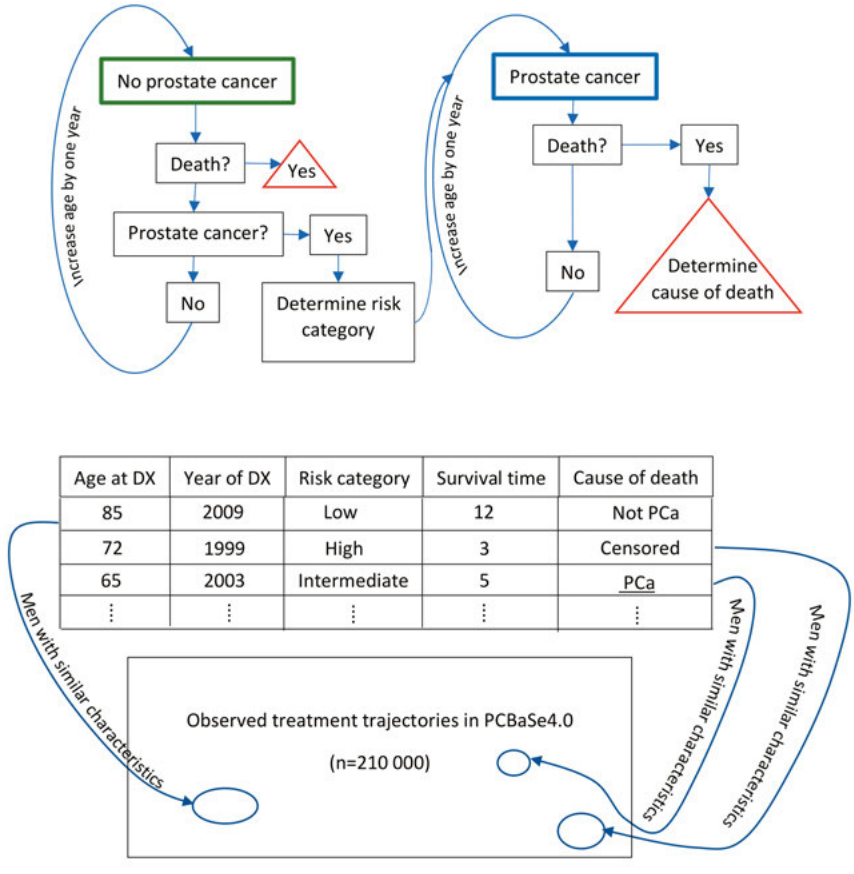

Figure 3. Schematic presentation of how the PRISM-PC-model simulation works. DX = Diagnosis; PCa = Prostate Cancer. Illustration by Westerberg M.

The model functions by first estimating the future incidence of prostate cancer based on the historical incidence of low- and intermediate- prostate cancer in a specific population. Thus, the incidence of low- and intermediate- prostate cancer acts as a proxy for the level of diagnostic activity in that specific population. The model then simulates a future scenario based on that data and creates a database containing prostate cancer cases, year of diagnosis, age at diagnosis, and risk category (low, intermediate, high, locally advanced, and distant metastasized). Each of these simulated prostate cancer cases are then randomly paired with an existing prostate cancer case with the same age, year of diagnosis, and stage of disease from the national prostate cancer registry to simulate treatment trajectories.

The end result is a large, simulated dataset of men, complete with age, year of diagnosis, risk category, treatment, and mortality. This dataset is then compared to the real, observed data over the same time period, 1996–2016.

Due to the fact that there were both lead-time effects on survival and changes in treatment strategies during the study period, we could not obtain a correct estimation on mortality for the simulated data. Therefore, we performed two extreme analyses. One where men had the same lead-time and treatment effects as corresponding men from the observed data, which underestimates the mortality; and one extreme, where the men did not benefit from any lead-time effects or improvements regarding treatment over these 20 years, which would overestimate the mortality. None of these are accurate, but the true value must lie somewhere in between, assuming that the prostate cancer care improves over time.

Statistical analysis

Incidence, treatment prevalence, and mortality are presented as the mean per year and per 100,000 men, from 1996 to 2016, age-standardized (age distribution of men 40–100 years in 2016). The incidence rate ratio (IRR) for mortality was analyzed by comparing the incidence rate in the observed data with each of the extreme scenarios for the simulated data.

Methodological considerations

The foundation of these studies was the population-based material that we created at the beginning of the project. It was a long process from start to finish as I began by trying to understand these men's perspective of their disease through interviews, which we later used to design the questionnaire.

We chose a population-based approach to minimize the risk of selection bias and sent the questionnaire to all Swedish men who received the diagnosis of low-risk prostate cancer during a specific year. The main strength here was that we could relatively easily scale up and approach a larger number of men to gain statistical power. However, as this was an observational study, there were various selection mechanisms that we could not account for.

The first, study-specific part of the questionnaire allowed us to ask the men a broad range of questions that are not typically included in publicly available, validated questionnaires. We chose this approach to get a better understanding of how it feels to be diagnosed and to live with prostate cancer. The downside to a study-specific questionnaire is that the answers might not be directly comparable to the results of other studies using different questionnaires. In the study-specific part of the questionnaire, no summary scores were used. Instead, each self-reported question was assessed individually.

In the second part of the questionnaire, we used EPIC-26 (short form) which is a validated instrument commonly used in urological research to assess functional outcomes after treatment for prostate cancer (erectile function, urinary bother, urinary incontinency, bowel related symptoms). A summary score ranging from 0-100 is calculated for each of these domains where 100 represents the best possible functional outcome.[59]

When designing a questionnaire, there are many things to consider. The questions have to be valid and yield answers as intended; moreover, the questionnaire has to be short and interesting enough to get a high response rate.[64] In our case, we chose to face-validate the questionnaire with a researcher accompanying several men while they completed the questionnaire. This was done to identify questions that were hard to understand or that could be misinterpreted.

Further, the questionnaire has to address the research questions. In our case, we deliberately included numerous questions to approach the disease from different angles, even though there was a risk of a lower response rate.

Data on cancer characteristics and information on treatments were retrieved from the NPCR, which is a nationwide registry with almost complete

coverage.[65] Sweden has an advantage when it comes to national registries and how they are linked together. One example is the Prostate Cancer Database Sweden (PCBaSe), where NPCR is linked to other registries, for example, Prescribed Drug Registry, the Patient Registry, and the Cause of Death Registry. This database and others similar to it provide unique opportunities for epidemiological research.

Missing data were handled by multiple imputations based on the method of chained equations to gain statistical precision.[66] Briefly, imputation means that missing values are replaced with values based on the observed data. There are several methods of imputation; however, we used the method of chained equations, were several copies of the original dataset are created and the missing values are replaced in each copy using a MICE-procedure.[67] Thereafter, these copies are combined into a final dataset without missing values. It is important to note that no outcomes were imputed. It is also important to note that imputation does not help regarding systematic error.

To minimize the issue of differences between responders and non-responders we worked hard to the maximize the response rate and performed a drop-out analysis, which did not show any major differences between the responders and non-responders. There is also an issue of recall bias as the questionnaires were administered seven years after diagnosis, which we had no effective way of accounting for. However, the relatively long time between diagnosis and completion of the questionnaire was necessary to obtain long-term follow-up data.

In an observational study like ours, there is no way to eliminate all confounding. However, there are ways to minimize them. The first step is to identify potential confounders, for example, by the use of directed acyclic graphs (DAGs),[62] which is a graphical tool to better visualize and understand the association between exposure and outcome.

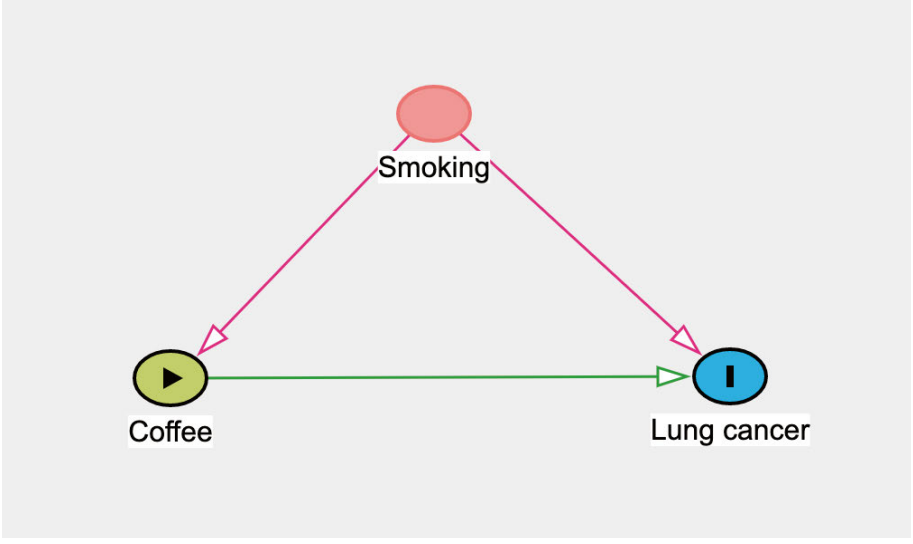

Figure 4. A simple example of a directed acyclic graph, where a possible association between coffee (exposure) and lung cancer (outcome) is likely explained by smoking (confounder). Picture from Daggity.

Known confounders, identified by DAGs, can be statistically adjusted for if there is sufficient data on that particular confounder. In our case, this was done by the use of logistic and ordinal logistic regression.

Ethical considerations

There are always ethical considerations when designing and conducting a study. First and foremost, we should not subject participants to any harm. Here, the questionnaire might be a painful reminder of the cancer diagnosis. Second, the privacy and anonymity of the participants must be ensured. This was achieved by handling and presenting data in such a way that individual participants could not be identified. It is also important to have transparency with regard to affiliations and funding, and all potential conflicts of interest should be declared. Here, there were no conflicts of interest.

The Regional Ethical Review Board at Uppsala University approved papers I–III (approval number 2014/278) and the Research Ethics Board at Umeå University approved paper IV (approval number 2016/239).

Results

Paper I

Among the 1,720 men who were invited, 1,288 men (75%) responded. This is a high response rate for such a study.

Among all participants, 958 (74.4%) reported a high overall satisfaction with care. High participation in decision-making (OR 4.18, 95% confidence interval [CI] 2.61–6.69), receiving more information (OR 11.1, 95% CI 7.97–15.6), high-quality information (OR 7.85, 95% CI 5.46–11.3), access to a nurse navigator (OR 1.80, 95% CI 1.44–2.26), and better functional outcomes (defined as 25 points higher on the EPIC-26 questionnaire; OR 1.34, 95% CI 1.21–1.48) were associated with a higher overall satisfaction with care.

Whether a doctor or specialist nurse conducted the follow-up (OR 0.84, 95% CI 0.66–1.07) did not affect the overall satisfaction with care.

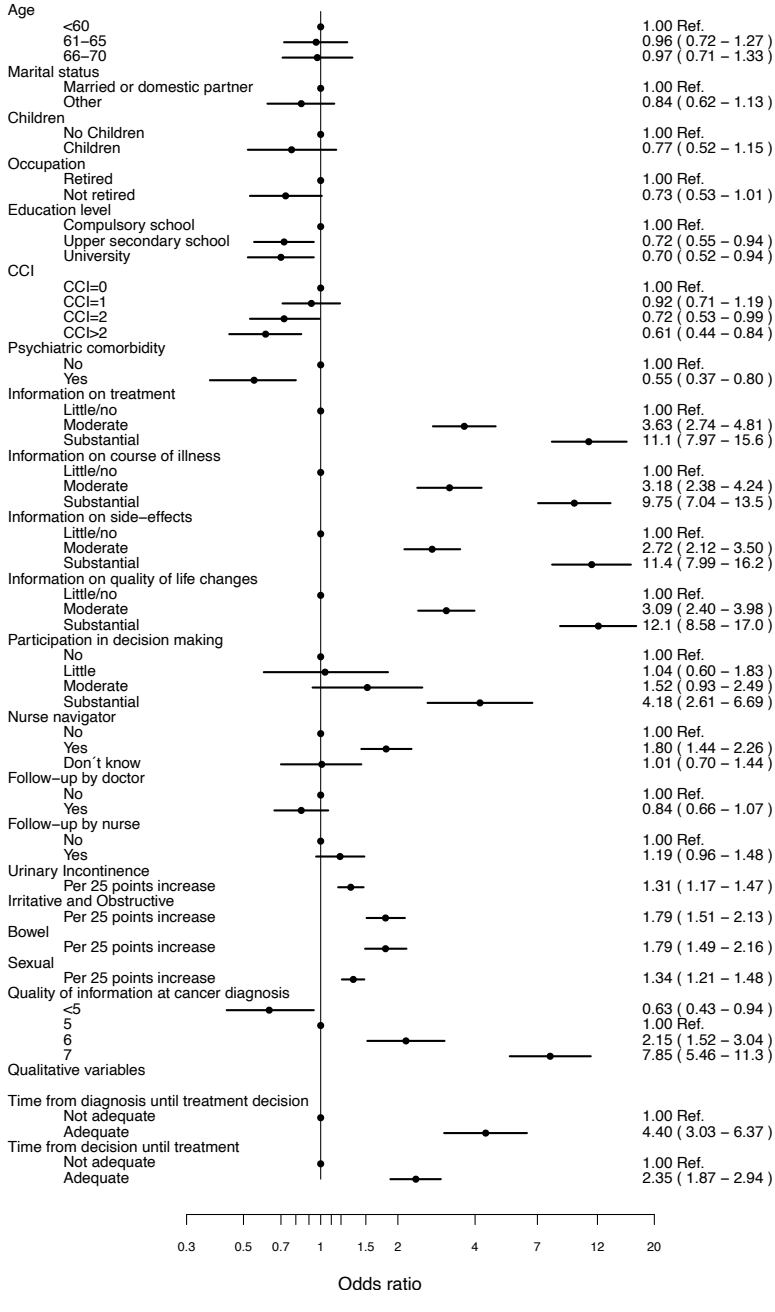

Figure 5. Forest plot, showing odds ratios (95% confidence interval) indicating the probability of a higher overall satisfaction with care. Adjusted for age, marital status, fatherhood, profession, education, Charlson comorbidity index (CCI), and psychiatric comorbidity. Ref. = reference.

Men who had undergone radical prostatectomy or radiotherapy reported a high overall satisfaction with care more often than men on active surveillance (78.2% vs. 84.0% vs. 72.6%), high participation in decision-making (70.5% vs. 64.5% vs. 49.2%), and having received more information (40.5% vs. 45.8% vs. 28.6%), and were less likely to believe that they would die from prostate cancer (3.8% vs. 3.9% vs. 8.0%).

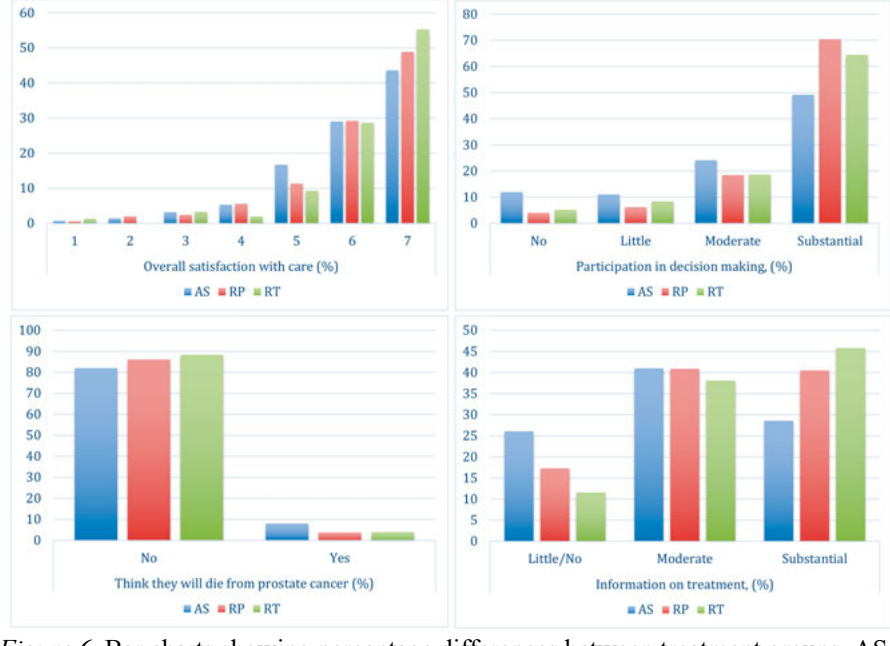

Figure 6. Bar charts showing percentage differences between treatment groups. AS = active surveillance; RP = radical prostatectomy; RT = radiotherapy.

Paper II

Among responders, 451 (35%) chose AS and 837 (65%) underwent immediate curative treatment; in addition, 238 (53%) of those who started on active surveillance were diverted to treatment within 7 years.

The most common reason for choosing active surveillance (83% of men on active surveillance) was explained as 'My doctor recommended AS.'

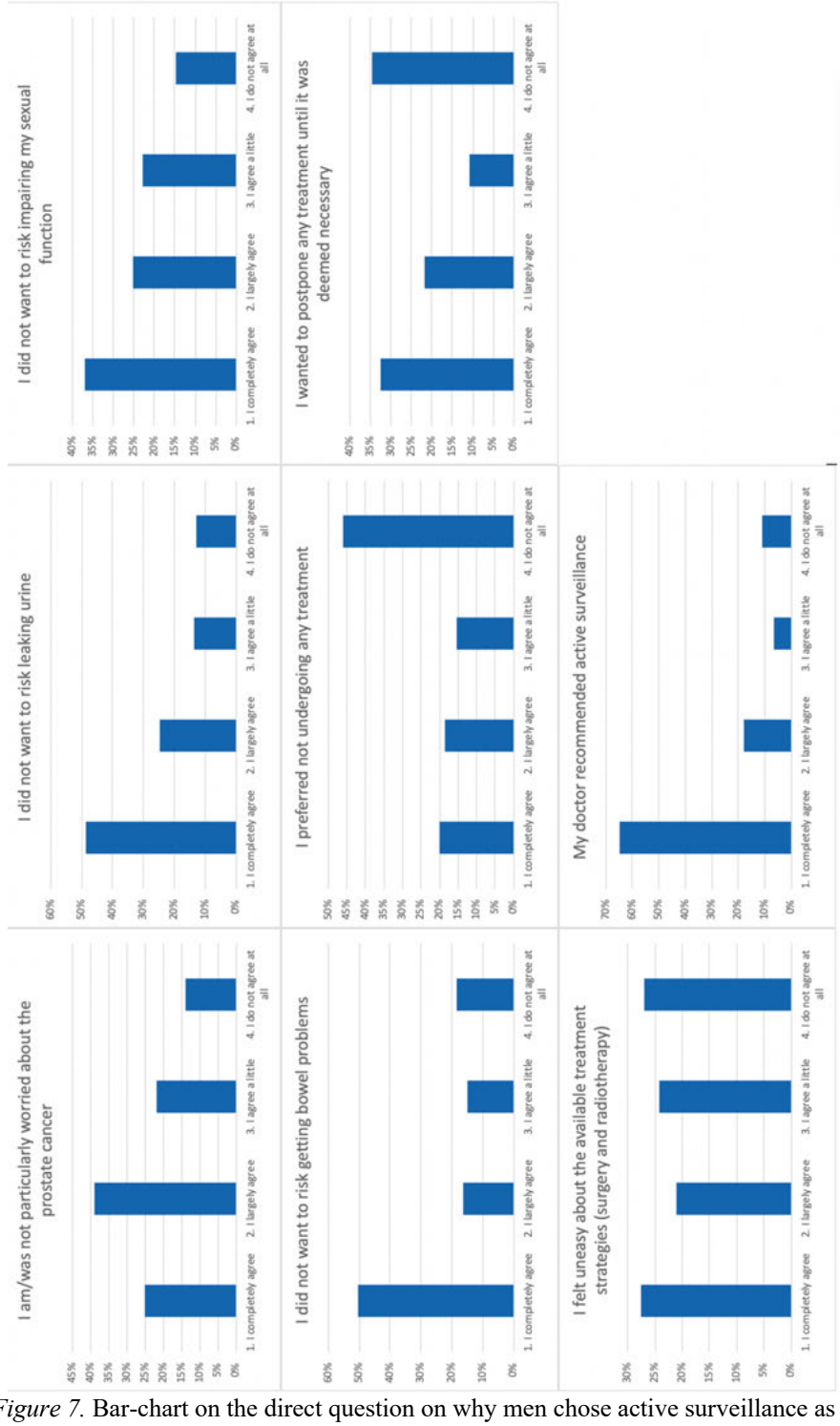

Figure 7. Bar-chart on the direct question on why men chose active surveillance as their primary treatment. Numbers are frequencies with percentages.

Older men (OR 1.81, 95% CI 1.29–2.54), a Charlson Comorbidity Index >2 (OR 1.50, 95% CI 1.06–2.13), and being unaccompanied when notified of the cancer diagnosis (OR 1.45, 95% CI 1.11–1.89) were associated with choosing active surveillance overtreatment.

Men were less likely to adhere to AS (OR 0.26, 95% CI 0.10–0.63) if they had a higher prostate-specific antigen (PSA) result at the time of diagnosis. The reason for diverting from active surveillance to curative treatment was 'the PSA level was rising' in 55% of the cases and biopsy findings in 36% of the cases.

Paper III

A total of 279 (22%) men reported a positive lifestyle change regarding diet or exercise. More side effects from treatment were associated with exercising less (OR 1.6, 95% CI 1.2–2.1) and being less interested in social activities and relationships (OR 1.8, 95% CI 1.5–2.1). A generally higher quality of life was reported among men who exercised more (OR 7.9, 95% CI 4.4–14) and men who had an increased interest in relationships and social activities (OR 5.2, 95% CI 2.1–13).

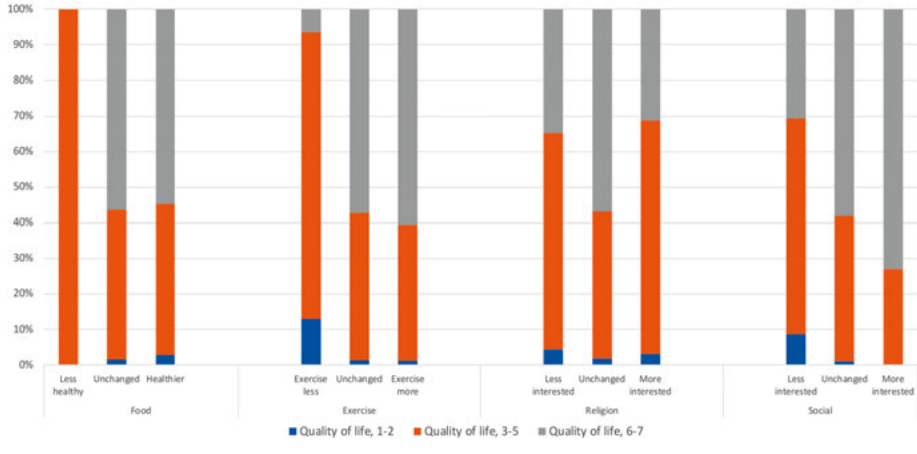

Figure 8. Bar chart illustrating lifestyle changes among men who rated their quality of life as low (1–2), moderate (3–5), or high (6–7).

Paper IV

A high diagnostic activity predominately increased the incidence of low and intermediate-risk prostate cancer. The number of low and intermediate cases was 48% higher in the scenario with high diagnostic activity.

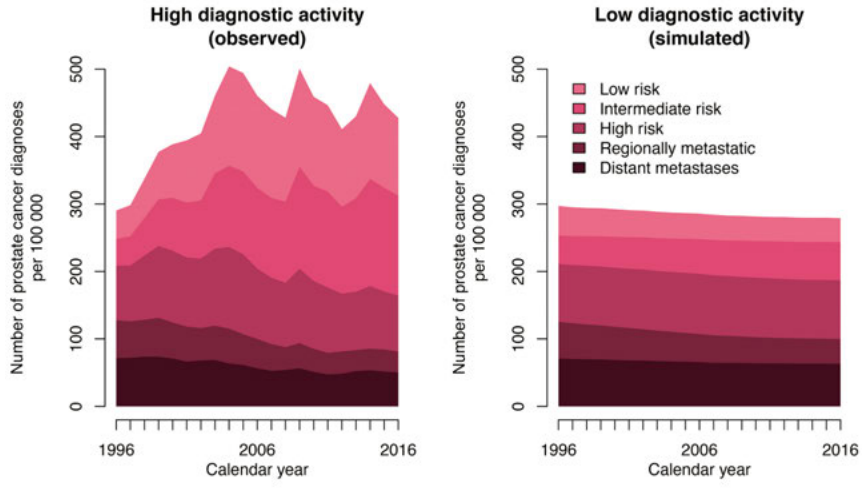

Figure 9. Incidence of prostate cancer by risk category, per 100,000 men, age-standardized (age distribution of men 40–100 years in 2016).

This resulted in a large increase in the number of men receiving deferred and curative treatment, with 78% more men receiving deferred treatment and 106% more men receiving curative treatment in the scenario with a high diagnostic activity.

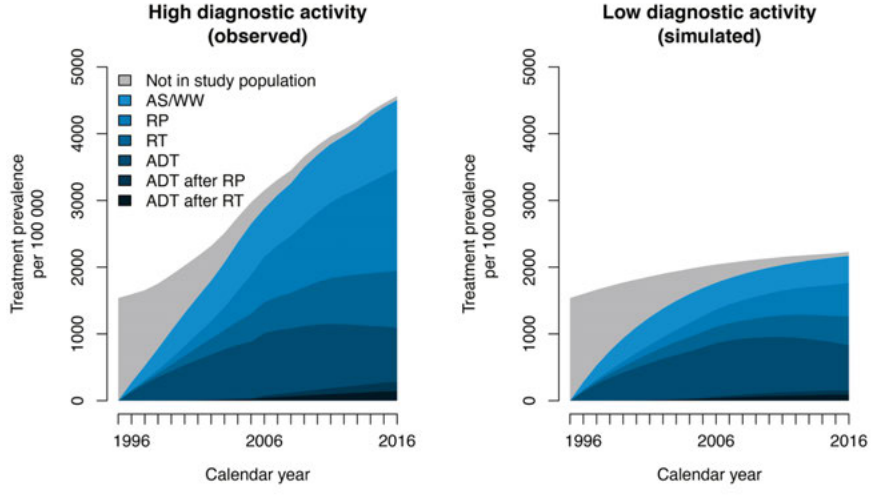

Figure 10. Prevalence of treatments for prostate cancer per 100,000 men, age-standardized (age distribution of men 40–100 years in 2016). AS/WW = Active surveillance/Watchful waiting; RP = Radical Prostatectomy; RT = Radiotherapy; ADT = androgen deprivation therapy.

Only modest differences were seen in advanced or metastasized disease and in prostate cancer mortality between the two scenarios, with somewhere

between 0 and 15% less prostate cancer specific deaths in the scenario with a high diagnostic activity.

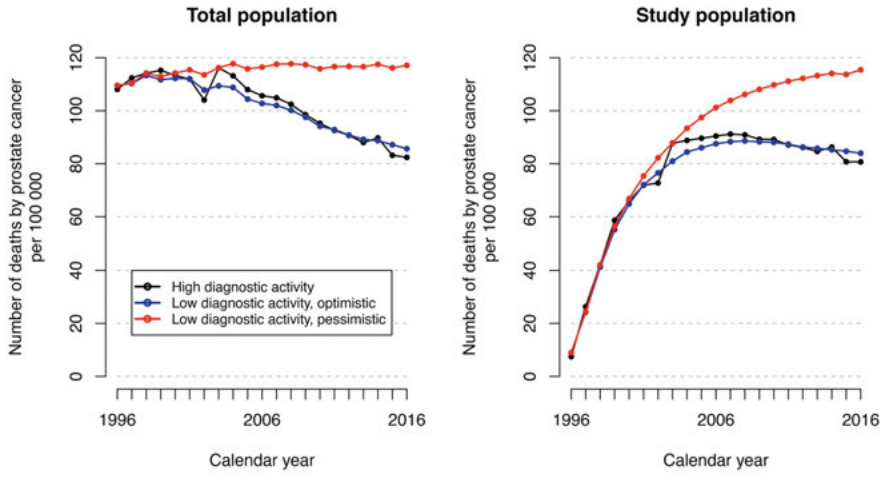

Figure 11. Prostate cancer specific death per 100,000 men, age-standardized (age distribution of men 40–100 years in 2016). Prevalent cases with diagnosis before 1996 included in the left figure.

Discussion

Paper I

In our first paper on satisfaction with care among men with prostate cancer, we found that a majority of men in our population (75%) reported high overall satisfaction. This is, of course, gratifying for the Swedish prostate cancer care where a lot of effort goes in to the management of prostate cancer.

However, as the study was made among men with low-risk disease with long-life expectancy and a few side effects from the disease itself, the degree of satisfaction might have been lower if we looked at the entire population of prostate cancer patients. Nevertheless, the men with low-risk disease represents a large proportion of the total number of men with prostate cancer, and due to the long life-expectancy, an even greater proportion when considering life-years lived with the disease.

Further, maintaining a high satisfaction among these men might be especially difficult as low-risk disease poses a particular educational challenge. This is because it is mainly managed by active surveillance where men are monitored and treated only in the event of disease progression, which might seem counterintuitive as the cancer is not urgently removed.

Several factors were identified as being associated with a higher overall satisfaction with care. The most notable factors were directly connected to the relationship between the patient and healthcare professionals such as a higher participation in decision-making and more information regarding the disease and possible treatments.

An aspect that was not discussed in the article is that men with psychiatric comorbidity experienced that they had received less information and that they were less participatory than other men in the population. It is impossible to determine whether these men actually received less information or if they had more difficulty assimilating the information received. Likely both.

An aspect that is often discussed and extensively researched is the relatively high morbidity associated with prostate cancer treatment. Both radical prostatectomy and radiotherapy are associated with major side effects such as urinary leakage, sexual dysfunction, and bowel symptoms.[25] In our study, poor functional outcomes after treatment were associated with a lower overall satisfaction with care. This finding was more or less expected; however, it was more surprising that the factors associated with the relationship between healthcare professionals and patients such as a higher participation in

decision-making or more information probably had a larger impact on satisfaction with care. This further highlights the importance of these, sometimes overlooked, aspects of managing prostate cancer.

Interestingly, men on active surveillance reported a lower overall satisfaction with care than men who were readily treated for their prostate cancer. They also reported receiving less information and being less participatory in the decision-making. This is probably a result of the educational difficulties surrounding active surveillance and highlights the importance of properly managing and informing these men.

We believe that this is the first article that shows that the involvement of nurse navigators improved the overall satisfaction with care. Nurse navigators are now a recommended part of the prostate cancer care, according to Swedish national guidelines. Involving nurse navigators is an excellent way to increase the accessibility as well the information and support provided to these men.

Paper II

Our second paper focused on choice and adherence to active surveillance. As active surveillance is one of the most important tools to reduce the overtreatment of low-risk disease, this is an important topic. Sweden has come a long way in this regard and has a very high uptake on active surveillance, almost 90%.[2] However, this varies between countries as well as between practices and urologists. In an American study from 2017, for example, the median use of active surveillance for eligible men was 57%; however, the use of active surveillance for eligible men varied between 0 and 96% among individual urologists.[68]

The example above corresponds well to our first finding, namely that a doctor's recommendation was the strongest predictor for choosing active surveillance. Generally, patients do as the treating physician tells them, so if we want to increase the uptake on active surveillance, we have to get doctors to recommend this strategy. Sweden has succeeded in this aspect, largely because active surveillance has clearly been the recommended strategy for low-risk prostate cancer for a long time according to national guidelines.

Another aspect that influenced the choice of treatment was age and concurrent diseases, where older men with more concurrent diseases were more likely to be managed with active surveillance. We cannot rule out the possibility of misclassification here, where some of these men might be on watchful waiting, meaning that men are closely watched and given palliative treatment in the event of disease progression.

An interesting and unexpected finding was that men who came alone (as opposed to with a family member or a friend) when they were notified of their cancer diagnosis were more likely to opt for active surveillance. It is important to note that these men were diagnosed back in 2008 when active surveillance

was still not as widely accepted as it is today. It is not easy to accept living with an untreated cancer and to trust the treating physician who says that the tumor is likely not going to progress.[69,70] It can be speculated that it is harder to assure an entire family than a single person, especially at the beginning of the surveillance era.

PSA was the strongest predictor of adherence to active surveillance which is another interesting finding. As discussed above, introducing PSA was a game changer for the management of prostate cancer. The diagnostic activity increased rapidly, resulting in an immense increase in the number of diagnosed and treated men. PSA has long been an important factor to consider as a urologist when managing prostatic disease and continues to be even today. However, PSA is far from perfect: a low PSA does not rule out prostate cancer, a high PSA does not necessarily equal prostate cancer, and a rising PSA during surveillance does not always reflect a progression in the disease.[71] Therefore, there is a need for caution when surveying men with low-risk prostate cancer, i.e., they should not be scheduled immediately for surgery or radiotherapy at first sight of a rising PSA. More information is needed before proceeding to treatment options in order not to overtreat these men, for example, an MRI followed by guided biopsies to confirm disease progression.

Paper III

In our third paper, we focused on lifestyle changes and quality of life. There is increasing evidence that lifestyle changes can improve both the risk of cancer recurrence and cancer specific death.[53-57] Thus, making lasting lifestyle changes is incredibly beneficial for prostate cancer patients. Further, evidence suggest that positive lifestyle changes might increase the general quality of life.[72] In previous studies the number of men who change their lifestyle following a diagnosis of prostate cancer is relatively low.[73] In our study, about one-fifth of the men reported making a positive lifestyle change. Whether this is low or high can be debated; however, we consider this to be a substantial number of men. Especially since these men changed their lifestyle without the aid of any structured interventions.

As discussed above, morbidity associated with prostate cancer treatment is often severe. For example, my first paper show that it reduces the overall satisfaction with care. In this paper, men who experienced more side effects from treatment were less likely to engage in lifestyle change, particularly regarding social relations and exercise. It can be speculated that side effects such as urinary leakage make life a lot more difficult, in terms of moving around freely or being relaxed when socializing. These results are congruent with a study by Stone et al. who found men with urinary leakage were less likely to engage in physical activity.[74]

Quality of life is an important aspect of healthcare in general, and cancer care in particular, as quality of life involves so many aspects of life, including psychological, physical, and social. The overall quality of life among the men in our study was relatively high; over 50% of our population rated their quality of life as high, and less than 2% as low.

We did not discuss an interesting aspect of our third paper, the impact of a cancer diagnosis on social relations. A cancer diagnosis could lead to a crisis, causing a person to withdraw from social relations due to anxiety or time-consuming treatments. On the other hand, a cancer diagnosis is a life-changing and difficult event that requires more social support than ever before. In the article, we focused on the 9% that decreased their interest in relationships and social activities; however, 2% responded that they increased their interest. It would be interesting to see what caused these men to go one way or the other, but the number of men who increased their interest is likely to be too small to draw any firm conclusions.

Our last research question for this article was whether lifestyle changes impacted the overall quality of life, which it did. Men who made a positive lifestyle change reported a high quality of life more often. Men who exercised more reported a higher general quality of life, which highlights the importance of a healthy lifestyle. An important note here is that the question on lifestyle change was if their diagnosis of prostate cancer had led to a lifestyle change, and the question on quality of life referred to the past 4 weeks; thus, it is likely that the lifestyle change came before the assessment of quality of life.

Paper IV

In our fourth paper, we used a simulation model to evaluate the PSA driven diagnostic activity over the past 20 years by comparing the real, opportunistic diagnostic activity to a simulated scenario with a more restrictive diagnostic activity.

We found that an increased diagnostic activity resulted in more men being diagnosed with prostate cancer. However, this increase was mainly seen in low- and intermediate-risk cases, which represents a substantial overdiagnosis, as the vast majority of these men would not have died from prostate cancer even without treatment.[4] It is also of interest to note that the diagnostic accuracy of transrectal ultrasound guided biopsies, which is the standard method of detection, is poor. Hence, the number of men who have undergone biopsies is likely much higher.[22]

The increase in the number of low- and intermediate-risk cases led to overtreatment, with twice as many men who received radical prostatectomy or radiotherapy in the scenario with a high diagnostic activity. Both of these treatments are associated with serious side effects, including erectile dysfunction, urinary leakage, and bowel problems. Thus, this overtreatment should not be

taken lightly.[30] Despite these large differences, relatively modest differences were seen in prostate cancer specific death.

This is the first article that quantifies the impact of the PSA driven diagnostic activity in detail for a country why these are interesting findings. It is important to point out that we do not claim that these are precise data, but an overview due to the use of a simulation model.

Our study evaluates the PSA driven diagnostic activity rather than the introduction of the PSA-testing specifically. Previous studies have evaluated the effects of the introduction of PSA-testing, but mostly by comparing data before and after its introduction.[75-80] There are also studies that use simulation models, but they generally evaluate the effects of PSA screening.[49,81-83] What our study adds is a quantification of the scale of the overdiagnosis and overtreatment.

To summarize this study, it is evident that the PSA driven diagnostic activity has saved lives, but at the cost of immense overdiagnosis and overtreatment. Was it worth it? A question that is almost impossible to answer. I think that the important lesson here is that new diagnostic tools like PSA should be introduced into clinical practice with caution and in an organized manner. Accordingly, the effects might be substantial.

Conclusions

To conclude this thesis,

Generally, men diagnosed with prostate cancer are satisfied with the care they receive. Information and participation in decision-making are key factors to improve overall satisfaction. However, men on active surveillance are less satisfied than men who receive immediate curative treatment. Accordingly, they need to be better informed and to be more participatory in their care.

Regarding choice of and adherence to active surveillance, a doctor's recommendation weighs heavily when deciding upon treatment. So, in order to increase the uptake on active surveillance, we need to convince doctors to recommend this treatment strategy. Rising PSA was the most common reason for diverting from active surveillance to curative treatment, even though this is a poor marker for disease progression.

A substantial number of men change their lifestyle after a prostate cancer diagnosis, even without the aid of structured interventions, which is why we consider this to be a teachable moment. However, poor functional outcomes after prostate cancer treatment reduce the willingness to engage in lifestyle changes; hence, it is important to support and rehabilitate these men. Finally, positive lifestyle changes improve the men's overall quality of life.

In paper IV, we found that the increased diagnostic activity for prostate cancer during the past 20–30 years has resulted in a large number of new prostate cancer cases, predominately low- and intermediate-risk cases. This has led to a substantial increase in the number of men receiving curative treatment but has only had modest effects on prostate cancer specific mortality.

Future perspectives

There are several dimensions to "future perspectives." There is the future regarding the data that we collected throughout this project, there is the aspect of my future as a researcher, and there is the future regarding the prostate cancer disease. I will touch on all three.

First, this dataset from papers I to III holds great potential. It contains population-based material with many interesting questions and an excellent response rate for a dataset of its kind. There are several areas still to be explored and we are looking at possibilities for future studies such as anxiety in regards to follow-up and a possible exaggerated fear of disease progression.

Second, regarding my future as I researcher, I will start by saying that I have really enjoyed this journey. It has been a long journey, involving a lot of hard work, but I have learned a great deal in the process. I also find that combining research with clinical work is greatly beneficial as it helps me keep a critical mind to what I am doing as well as to raise questions for future research. My hope and ambition is to continue with research after my doctoral studies come to an end.

Third, regarding the future of prostate cancer research, there is no lack of ongoing work as this is the most common cancer among men worldwide and an enormous research field with almost 10,000 publications annually on PubMed. There are several areas of interest for future research such as genetics, prevention, early detection, staging, treatments, and follow-up.

One of the main research questions regarding prostate cancer is the heterogenicity of the disease; how do we get better at distinguishing between high- and low-risk cases at an early stage in order to treat only when necessary?

Much has happened in recent years regarding the diagnostics and treatment of prostate cancer. Better diagnostic tests combining clinical, genetical, and protein markers have emerged for better accuracy; MRI has become the standard of care for prostate cancer, offering better diagnostic precision. Active surveillance has become the standard of care for low-risk disease and is gaining acceptance worldwide. Focal treatments for prostate cancer, where only the tumor bearing parts of the prostate, are treated are being tested in clinical practice. Regarding advanced disease, treatments have become more aggressive with, for example, early chemotherapy, radiotherapy for the primary tumor, and second generation hormonal treatments, resulting in better survival for men with metastatic disease.

Sammanfattning på svenska

Bakgrund

Prostatacancer är en heterogen sjukdom som generellt har låg dödlighet och lång förväntad överlevnad men där det inte sällan förekommer svåra fall med mycket aggressiv sjukdom som snabbt ger metastaser. Det är den här spridningen i svårighetsgrad som gör prostatacancer så komplicerat. Hur hittar vi dom aggressiva fallen utan att överdiagnostisera och därmed även överbehandla de lindrigare fallen? En hög diagnostisk aktivitet ger en överdiagnostik och överbehandling medan en underdiagnostik kommer att missa svåra fall som hade kunnat botas om dom hittats tidigt. Det sker en snabb utvecklig på området med nya diagnostiska metoder och nya behandlingar. I dessa arbeten har vi försökt att ta ett helhetsgrepp på prostatacancersjukdomen och undersökt effekter av både diagnostik och behandling.

Arbete I

I det första arbetet har vi försökt skapa en bild av hur nöjda patienterna är med sin prostatacancervård samt vilka faktorer som påverkar deras nöjdhet för att på så sätt förstå vad som behöver förbättras.

Arbetet är baserat på ett material där alla svenska män, 70 år eller yngre, registrerade i Nationella prostatacancerregistret, som diagnostiserades men låg-risk prostatacancer under 2008 och som senare genomgick aktiv uppföljning, operation eller strålning av prostatakörteln bjöds in att svara på en omfattande enkät. Totalt 1720 män bjöds in varav 1288 svarade (75%).

Vi fann att den totala nöjdheten bland män med låg-risk prostatacancer är hög, 74% rapporterade att dom var nöjda med vården som helhet och endast 2% var missnöjda. Vår studie visar att dom faktorer som ökar nöjdheten mest är tillräcklig information (OR=7.85, CI=5.46-11.3) samt delaktighet i beslut och behandling (OR=4.18, CI=2.61-6.69). Att ha tillgång till en kontaktsjuksköterska ökade nöjdheten (OR=1.80, CI=1.44-2.26) och det spelade inte någon roll för nöjdheten huruvida uppföljningen utfördes av en läkare (OR=0.84, CI=0.66-1.07) eller sjuksköterska (OR=1.19, CI=0.96-1.48).

Män som genomgått behandling för sin prostatacancer var i högre utsträckning nöjda med sin vård (operation, 78%, strålning 84%) än dom som går i

aktiv uppföljning (73%) varför män i aktiv uppföljning behöver få mer information och bli mer delaktiga i sin vård.

Arbete II

I det andra arbetet undersökte vi hur många av männen som väljer att gå i aktiv uppföljning för sin prostatacancer (vilket är den rekommenderade strategin för behandling av låg-risk prostatacancer) istället för att genomgå behandling direkt och varför dom väljer det ena eller det andra. Målet var att förstå vad vi behöver fokusera på för att öka andelen som går i aktiv uppföljning.

Arbete II är baserat på samma material som arbete I och visar att 35% av männen valde aktiv uppföljning och 65% behandlades direkt. Av männen i aktiv uppföljning gick 53% till behandling inom 7 år. De flesta män valde aktiv uppföljning pga. läkarens rekommendation (83%). Äldre män (OR 1.81, 95% CI 1.29-2.54), män med en ökad samsjuklighet (OR 1.50, 95% CI 1.06–2.13) och som inte hade någon anhörig med sig vid cancerbeskedet (OR 1.45, 95% CI 1.11-1.89) valde oftare aktiv uppföljning. Män som diagnostiserades under utredning av nedre urinvägssymtom istället för genom PSA provtagning utan symtom valde oftare aktiv uppföljning (OR 1.78, 95% CI 1.16-2.72).

Den viktigaste faktorn för huruvida man stannar i aktiv uppföljning eller inte var PSA. Män med högre PSA vid diagnos hade lägre sannolikhet att stanna i aktiv uppföljning (OR 0.26, 95% CI 0.10-0.63). I 55% av fallen angavs ett stigande PSA som en bidragande orsak till av aktiv uppföljning avbröts till förmån för botande behandling.

Sammanfattningsvis så har sjukvårdens attityd mot aktiv uppföljning stor påverkan på val av behandling och PSA stor påverkan på i vilken utsträckning män stannar i aktiv uppföljning.

Arbete III

I vårt tredje arbete fokuserade vi på livsstilsförändringar efter en prostatacancerdiagnos, vilka faktorer som bidrar till om man genomgår en livsstilsförändring och huruvida en positiv livsstilsförändring leder till bättre livskvalitet.

Tidigare forskning har visat att positiva livsstilsförändringar förbättrar livskvalitén, minskar risken för återfall av cancersjukdomen och minskar dödligheten i cancer [53-57,72].

Arbetet som baserades på samma material som arbete I och II visade att 279 (22%) av männen hade genomgått en positiv livsstilsförändring. Män som hade flera biverkningar efter behandling motionerade mindre (OR 1.6, 95% CI 1.2-2.1) och var mindre intresserade av sociala aktiviteter (OR 1.8, 95% CI 1.5-2.1). Män som motionerade mer (OR 7.9, 95% CI 4.4-14) eller som

intresserade sig mer för sociala aktiviteter (OR 5.2, 95% CI 2.1-13) rapporterade en högre livskvalitet.

En relativt stor del av män som diagnosticeras med prostatacancer genomgår en livsstilsförändring vilket är positiv i och med att livsstilsförändringar även höjer livskvaliteten. Dock så minskar biverkningar efter behandling sannolikheten att genomgå livsstilsförändringar varför det är viktigt att stötta och rehabilitera dessa män.

Arbete IV

I vårt fjärde arbete utvärderade vi effekterna av den PSA drivna diagnostiska aktiviteten som har ökat stadigt under de senaste 20–30 åren. Vi använde oss av en ny datorsimuleringsmodell (PRISM-PC) för att jämföra verkligheten med ett simulerat scenario med en lägre diagnostisk aktivitet.

Vi fann att 48% fler män har fått en prostatacancerdiagnos på grund av den ökande diagnostiska aktiviteten. Av dessa var dock merparten låg eller mellanriskcancer med god överlevnad även utan behandling. Det stora antalet diagnostiserade män har resulterat i att 108% fler män har erhållit behandling (strålning eller operation). Trots det stora antalet behandlingar har effekterna på prostatacancerdödlighet varit relativt måttliga med någonstans mellan 0 (IRR 1.02 95% CI: 0.98-1.05) och 15% färre döda (IRR 0.85 95% CI 0.82–0.88).

Slutsatsen är att nya diagnostiska metoder skall införas organiserat och med försiktighet då konsekvenserna kan bli stora och inte är lätta att förutse.

Slutsatser

Den här avhandlingen om hur det är att diagnosticeras och att leva med prostatacancer har bidragit med kunskap om vad som krävs för att få nöjda patienter, nämligen delaktighet och tillräckligt med information.

Vidare har vi funnit att läkarens ord väger tungt när det kommer till val av behandling vilket innebär att om man vill öka andelen män i aktiv monitorering så måste man först få behandlade läkare att rekommendera strategin.

Avhandlingen har också bidragit med kunskap om livsstilsförändringar hos män med prostatacancer. Vi har kunnat konstatera att relativt stor del av männen genomgick en positiv livsstilsförändring som resultat av sin diagnos. Resultaten antyder att det här skulle kunna vara en bra tidpunkt för att på ett effektivt sätt genomföra livsstilsinterventioner. Vidare så har vi sett att män som upplever mer biverkningar efter sin behandling för prostatacancer i lägre utsträckning genomför positiva livsstilsförändringar vilket är ytterligare en anledning till att stötta och rehabilitera män efter behandling.

Vi har också konstaterat att den PSA-drivna diagnostiska aktiviteten under de senaste decennierna har lett till ett stort antal nya prostatacancerfall och ett stort antal män som genomgått kirurgi eller erhållit strålning men att effekten på dödlighet i prostatacancer har varit relativt blygsam varför nya diagnosiska metoder bör införas organiserat och med försiktighet.

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