Adverse effects of curative treatment of prostate cancer

Jón Örn Fridriksson
“I don’t pretend that we have all the answers. But the questions are certainly worth thinking about.”

Sir Arthur C. Clarke
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Abstract

**Background** Screening for prostate cancer is debated, there is conflicting data on the net benefit of screening. Men who consider screening need to be informed on the pros and cons. Rehospitalization after surgery can be used as an indicator of general quality of care. For radical prostatectomy, little is known on the readmission rate after surgery. Men diagnosed with low- and intermediate-risk prostate cancer have low prostate-cancer specific mortality. However, adverse effects after curative treatment can be severe and decrease quality of life. Curative treatments for prostate cancer differ mainly in the pattern of adverse effects but detailed analysis of long-term adverse effects is lacking.

The aim of this thesis was to assess the perioperative quality of radical prostatectomy and the risk of adverse effects after curative treatment for prostate cancer.

**Material and Methods** In this thesis, data from the National Prostate Cancer Register (NPCR) and other nationwide Swedish registers were used. By use of the Swedish personal identity number, NPCR was cross-linked to other registers creating Prostate Cancer data Base Sweden (PCBaSe), a large dataset for research.

**Results** The proportion of men who had received information on the pros and cons of screening for prostate cancer with PSA testing was low (14%) indicating that the majority of men who were screened did not make an informed decision. The risk of rehospitalization within 90 days after radical prostatectomy was approximately 10% and similar after retropubic and robot-assisted radical prostatectomy. Compared to controls, there was an increased risk of adverse effects after both radiotherapy and radical prostatectomy up to twelve years after treatment and the overall risk was quite similar after retropubic and robot-assisted radical prostatectomy.

**Conclusion** Improved information to men on the pros and cons of PSA screening is warranted. The risk of adverse effects was elevated up to 12 years after curative treatment for prostate cancer. The pattern of adverse effects was different after radiotherapy and radical prostatectomy but quite similar after retropubic and robot-assisted radical prostatectomy.
**Abbreviations**

- **BPH**: Benign prostate hyperplasia
- **CaPSURE**: The Cancer of the Prostate Strategic Urologic Research Endeavor registry
- **CCI**: Charlson comorbidity index
- **CombAT**: The Combination of Avodart and Tamsulosin study
- **ERSPC**: The European Randomized Study of Screening for Prostate Cancer
- **HIFU**: High-intensity focused ultrasound
- **ISUP**: International Society of Urological Pathology
- **IRR**: Incidence rate ratio
- **LISA**: Longitudinal Integration Database for Health Insurance and Labour Market Studies
- **LRP**: Laparoscopic radical prostatectomy
- **LUTS**: Lower urinary tract symptoms
- **MRI**: Magnetic resonance imaging
- **NOMESCO**: Nordic Medico-Statistical Committee
- **NPCR**: The National Prostate Cancer Register
- **OR**: Odds ratio
- **PCBaSe**: Prostate Cancer data Base Sweden
- **PCOS**: Prostate Cancer Outcome Study
- **PIVOT**: Prostate Cancer Intervention versus Observation Trial
- **PLCO**: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
- **PRIAS**: The Prostate Cancer Research International: Active Surveillance
- **ProtecT**: Prostate Testing for Cancer and Treatment
- **PSA**: Prostate specific antigen
- **RARP**: Robot-assisted radical prostatectomy
- **REDUCE**: The Reduction by Dutasteride of Prostate Cancer Events
- **RP**: Radical prostatectomy
- **RRP**: Retropubic radical prostatectomy
- **RR**: Relative risk
- **RT**: Radiotherapy
- **SEER**: The Surveillance, Epidemiology, and End Results Program
- **SELECT**: The Selenium and Vitamin E Cancer Prevention Trial
- **SPCG-4**: The Scandinavian Prostate Cancer Group Study Number 4
- **STHLM3**: The Stockholm 3 model
List of papers


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Populärvetenskaplig sammanfattning på svenska

Prostatacancer är den vanligaste cancersjukdomen i Sverige och medianåldern vid diagnos är 67 år. Varje år diagnostiseras ungefär 10,000 svenska män och 2,500 män dör av prostatacancer. Trots att prostatacancer kan vara en allvarlig sjukdom, är den oftast beskedlig och flesta män med prostatacancer dör av en annan orsak.


Enligt Socialstyrelsens nationella riktlinjer skall varje man som överväger att ta ett PSA prov få skriftlig information om fördelar och nackdelar med provet. I delarbete I undersökte vi hur många män som fått denna information och fann att endast 14% av männen informerats enligt Socialstyrelsens riktlinjer. Vidare fann vi att 10% av männen visste inte ens om att de tagit ett PSA prov.


Operation, så kallad radikal prostatektomi är ett alternativ för att bota prostatacancer som inte har spridit sig. Radikal prostatektomi kan utföras på olika sätt. Det är i huvudsak två metoder som nu används i Sverige, konventionell öppen operation, och robotassisterad prostatektomi. I
delarbete II jämförde vi resultatet efter dessa olika metoder genom att använda återinläggning efter kirurgi som ett mått på vårdkvalitet. Vi fann att återinläggningsfrekvensen inom 90 dagar efter operation var ungefär 10% och jämförbar mellan metoderna.

Biverkningar några år efter radikal prostatektomi och strålbehandling för prostatecancer är väl dokumenterade. Däremot finns det lite data om långtidsbiverkningar efter behandling. I delarbete III och IV analyserades biverkningarna up till tolv år efter kurativt syftande behandling. Genom att använda diagnoskoder och åtgärdskoder registrerade i Patientregistret och data från Nationella Prostatacancerregistret kunde vi analysera frekvensen av valda biverkningar efter behandling och jämföra risken för biverkningar mellan olika behandlingar. I delarbete III jämfördes risken mellan operation och strålbehandling och vi fann att risken för biverkningar kvarstod up till tolv år efter båda behandlingarna. Urininkontinens var mycket vanligare efter operation men tarmbesvär och vattenkastningsbesvär var vanligare efter strålbehandling. Flera biverkningar inträffade inom 3 år efter operation och totalt var risken för långtidsbiverkningar högre efter strålbehandling. I delarbete IV jämfördes på liknande sätt risken för biverkningar efter konventionell öppen radikal prostatektomi och robotassisterad radikal prostatektomi. Risken för flesta biverkningar var jämförbar mellan dom olika operationsmetoderna men risk för vattenkastningsbesvär var dock något högre efter öppen operation och risken för ett ärrbräck var högre efter robotassisterad operation.

Utifrån resultatet i detta arbete konkluderar vi att behandlingsalternativen har olika biverkningar både på kort och långt sikt. Detta kan ha klinisk betydelse vid val av behandling eftersom varje enskild patient måste vara beredd att acceptera risk för biverkningar som behandlingen innebär. Bättre kartläggnings av biverkningarna kan således vara till stor nytta för både patienter och vårdgivare vi val av behandling.
Background

The prostate

The prostate is a secondary sex organ with a size of approximately 20-30 mL and produces one third of the seminal fluid. Its secretion is alkaline and neutralizes the acidic environment in the vagina that leads to prolonged life of the spermatozoa and thereby increases the chances of fertilization. The only role of the prostate is linked to reproduction and thus most men only ‘need’ their prostate during the reproductive period of their life. The prostate is located deep in the pelvic cavity, surrounded by a number of small nerve fibres and vascular plexa and the most proximal part of the urethra passes through the prostate. The prostate usually grows with age and may cause bladder outlet obstruction. Many middle aged men suffer from lower urinary tract symptoms. Furthermore, neoplasia is common in the prostate. The unfortunate location of the prostate makes treatment for prostatic diseases difficult and often accompanied with damage to the sensitive nerve fibres and/or the urinary sphincter muscle causing adverse effects that can affect the man’s quality of life.

Prostate cancer

Prostate cancer is a common disease among middle aged men. It ranges from slow-growing disease without symptoms to fast-growing, possibly fatal disease that requires treatment. Localized prostate cancer usually causes no symptoms. More advanced cancer can cause haematuria or urinary obstruction and cancer that spreads outside the prostate gland may result in pain from bone metastases.

Epidemiology

Prostate cancer is the second most common cancer and the sixth leading cause of cancer deaths worldwide, with an estimated 899,000 cases and 258,000 deaths annually [1]. Incidence rates of prostate cancer vary more than 20-fold worldwide, likely due to difference in genetic and lifestyle factors but also different detection practices. The incidence rates are highest in the highest income regions of the world including North America, Western Europe and Scandinavia and lowest in Asia and Northern Africa [2].
Prostate cancer is the most common cancer among Swedish men, accounting for one third of all male cancer. Approximately 10,000 new cases are diagnosed and 2,500 men die from prostate cancer annually [3, 4]. Between 1960 and 1990 the incidence of prostate cancer rose steadily but in the late 1990s a sharp increase was observed in the incidence of prostate cancer, likely as a result of the introduction of PSA testing in Sweden. Since the early 2000s has the incidence fluctuated but remained relatively stable with incidence rates between 100 and 110 cases per 100,000 men. The prostate cancer mortality has been stable since 1960 but since 2000 a slow decline in the mortality has been observed (figure 1).

![Incidence and Mortality of Prostate Cancer in Sweden](image)

**Figure 1.** Age-standardized incidence and mortality of prostate cancer in Sweden between 1960 and 2014 [5].

Prostate cancer is rare in men younger than 50 years of age but the incidence rises sharply between age 50 and 65 year (figure 2). The median age at diagnosis is 67 years [6]. The average age of death from prostate cancer is 77 years and has remained stable over the last three decades [7]. Results from autopsy studies suggest that 27% and 34% of men in the fourth and fifth decades of age have histological prostate cancer, respectively. Furthermore, most men 85 year or older have histological prostate cancer [8].
Incidence of prostate cancer varies widely between ethnic populations and is highest among African-American people in the United States. Migration studies have shown that when Japanese men moved from Japan to the United States, their incidence of prostate cancer increased to about 50% of the rate for Caucasians people and to 25% of that for African-American men in the United States [9].

Epidemiological studies have shown that for men with family history of prostate cancer, the relative risk of prostate cancer is increased two- to fourfold [10]. However, increased diagnostic activity among relatives to men with prostate cancer may, at least partly, explain familial aggregation of prostate cancer [11]. In a recent study from PCBaSe, Bratt et al. reported that the relative risk of prostate cancer for brothers of men with prostate cancer was 3.1 but the risk decreased with age and at 75 years was the relative risk 2.4 [12]. Furthermore, men with two or more first-degree relatives with prostate cancer had higher risk of prostate cancer compared to men with only one first-degree relative with prostate cancer.

**Figure 2.** Age-specific incidence of prostate cancer in Sweden [5].
**Risk factors**

The only well-established risk factors for prostate cancer are old age, ethnicity and a family history of the disease. Prostate cancer has strong correlation with increasing age and only 25% of prostate cancer cases are diagnosed before the age of 65 in Europe [13].

**Hormones**

Androgens play an important role for normal growth, development and maintenance of the prostate. In the prostate, testosterone is converted to dihydrotestosterone with the enzyme 5α-reductase. Withdrawal of testosterone by surgical or medical castration is often used as a treatment of advanced prostate cancer and is effective in 75-80% of men with metastatic prostate cancer. However, although testosterone is necessary for the development of prostate cancer it appears that high serum testosterone level does not increase the risk of prostate cancer and a recent meta-analysis of prospective studies showed no association between physiological serum testosterone levels and risk of prostate cancer [14].

The insulin growth factor (IGF) system has been proposed as one link between the sedentary western lifestyle and prostate cancer. IGF is a peptide growth factor that regulates cancer cell proliferation and differentiation. A recent meta-analysis provided strong evidence that IGF-I is likely to be involved in prostate cancer development [15].

**Lifestyle**

A sedentary western lifestyle has been suggested as a possible risk factor [16]. In a large, prospective cohort study analysing data on metabolic factors from 289,866 men, high levels of BMI, blood pressure and a combination of metabolic factors were associated with a modest increase in the risk of prostate cancer-specific mortality. In contrast, these metabolic factors did not effect the risk of overall prostate cancer [17].

It is unclear how physical activity can effect the risk of prostate cancer. It is plausible that physical activity may reduce the risk of prostate cancer by influencing the levels of androgens, insulin and IGF-I. Furthermore, physical activity can prevent obesity and enhance immune function that could reduce risk of prostate cancer. Earlier studies on the association between physical activity and prostate cancer have been inconsistent. However, a recent meta-analysis of 88,294 cases showed an inverse association between physical activity and risk of prostate cancer but the decrease in risk was small [18].
Smoking has been suggested as a risk factor for prostate cancer [19]. This association seems to be stronger for aggressive or fatal cancer. Specifically, current heavy smokers appear to have higher risk of prostate cancer-specific mortality and recurrence [20].

Snus is a Scandinavian smokeless tobacco that users keep in their mouth for variable length of time. Snus contains nicotine but not the toxic chemicals of smoke that smokers inhale. In a nested prospective cohort study from Sweden, snus users had increased risk of prostate cancer mortality. Furthermore, among men with nonmetastatic disease was the risk of prostate cancer-specific death threefold as compared to men never using any type of tobacco [21].

**Chemoprevention**

Drugs and micronutrients have been suggested for chemopreventive use and although results from small-scale studies have been promising, larger randomised trials have failed to reproduce their findings. Currently, no chemopreventive method has been approved for systematic use in the general population but further research on this subject is warranted [22].

**Micronutrients**

Selenium and vitamin E are micronutrients that have been investigated as potentially protective for the development of prostate cancer. Selenium is a non-metallic trace element that inhibits tumorigenesis. Vitamin E is a fat-soluble vitamin that has antioxidant effects. Earlier studies have shown promising results for the use of selenium and vitamin E suggesting that intake of those micronutrients could be protective against prostate cancer. In a randomised double-blind, placebo controlled primary-prevention trial that randomised 29,133 male smokers in Finland to receiving placebo, vitamin E, beta carotene and both vitamin E and beta carotene, fewer cases of prostate-cancer were diagnosed among men that received vitamin E [23]. Another randomised, double-blind, placebo-controlled trial showed that selenium supplementation had protective effect on the overall incidence of prostate cancer [24]. However, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a recent randomised, double-blinded placebo controlled study that included over 35,000 men, showed that selenium or vitamin E, alone or in combination, did not prevent prostate cancer [25].

**5α-reductase inhibitors**

Dihydrotestosterone is the primary androgen in the prostate and is involved in the pathophysiology of prostate cancer. Thus, it is a plausible target for chemoprevention against prostate cancer. It has been suggested that
finasteride, a drug that inhibits the one of the two isoforms of 5α-reductase, may reduce the risk of prostate cancer. In the Prostate Cancer Prevention Trial (PCPT) 18,882 men were randomized to receiving finasteride or placebo. The results showed that finasteride reduced the risk of prostate cancer by approximately 25% but finasteride was also associated with a small, but statistically significant increase in the rate of high-risk prostate cancer [26].

Dutasteride is another 5α-reductase inhibitor but unlike finasteride, dutasteride inhibits both isoforms of 5α-reductase. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study is a randomised, double blind, placebo-controlled trial where 8,231 men were randomised to receive dutasteride or placebo. The results showed approximately 23% relative risk reduction of prostate cancer in the dutasteride group. However, as in the PCPT trial was the incidence of high-risk prostate cancer higher at 4 years after randomisation in the dutasteride group. During the first 2 years of the trial, 141 more men in the placebo group were excluded because of diagnosis of prostate cancer. The authors speculate that if these men had remained in the placebo group, a proportion of the cancers might have been upgraded on biopsies to high grade cancers at later follow-up. This might have resulted in smaller difference in high risk cancer between the groups [27].

A third study on the effect of chemoprevention with 5α-reductase inhibitor is the Combination of Avodart and Tamsulosin (CombAT) study. The study design was similar as in the PCPT and REDUCE trials. In total 4,844 men with symptomatic benign prostate hyperplasia (BPH) were randomised to receive dutasteride, tamsulosin or a combination of both. Primary end point was the time to acute urinary retention or BPH-related surgery. Detection of prostate cancer was a secondary end point of the study. Dutasteride, alone or in combination with tamsulosin, was associated with 40% relative risk reduction of prostate cancer with similar reduction in high- and low-grade cancer [28].

A recent large population-based case-control study based on data from PCBaSe reported similar findings as in the randomised controlled studies. Men treated with 5α-reductase had significantly decreased risk of prostate cancer but in contrast to the PCPT and REDUCE trials, no statistically significant increase in risk for high-grade cancer was observed [29].

It is uncertain if 5α-reductase inhibitors have any impact on prostate cancer-specific mortality as neither the REDUCE nor the PCPT trial planned for an extended mortality follow-up. However, Pinsky et al. used data from the
PLCO study to estimate the prostate cancer-specific mortality in the PCPT and REDUCE trials. The results showed no difference in prostate cancer-specific mortality in the treatment arms [30].

**Prostate specific antigen (PSA)**

PSA is a glycoprotein that was identified in human prostatic tissue in 1970. Another protein in the seminal fluid, semenogelin, causes the ejaculate to clot. The PSA has the role to lyse the clot but it is currently unknown why this clotting and lysis mechanism is important for the reproduction. The PSA is produced both in normal epithelial cells of the prostate and in prostate cancer cells. A small proportion of PSA leaks through the basement membrane and diffuses into the circulation. Prostate cancer causes disruption of the basement membrane and this appears to increase the PSA leak into the peripheral circulation resulting in elevation of serum PSA level. Elevation of serum PSA may be an indicator of prostate cancer but the PSA is prostate-specific but not disease-specific. Thus, substantial overlap in PSA values between benign and malignant prostate disease is a limitation for the use of PSA as a prostate cancer tumor marker [2].

PSA that enters the circulation is bound by protease inhibitors but a fraction circulates as free PSA. Men with prostate cancer have lower levels of free PSA in the peripheral circulation. Consequently, the ratio of free to total PSA, named the PSA index, is lower in many patients with prostate cancer and can aid in the discrimination between benign prostatic disease and prostate cancer.

To compensate for PSA elevation caused by BPH and prostate size, transrectal ultrasound has been used to measure prostate volume. Thereafter, PSA density can be calculated, with densities higher than 0.20 PSA/mL more suggestive of prostate cancer. However, variations in prostate shape limits the utilisation of this method as a screening test [31].

**Gleason grading**

The Gleason grading system was developed between 1966 and 1974 by Donald Gleason and the Veterans Administration Cooperative Urologic Research Group [32]. The Gleason score defines five different histologic patterns of prostatic adenocarcinoma ranging from 1 to 5 where 1 is the highest and 5 the lowest differentiated cancer. The most and second most common patterns are added resulting in a Gleason score ranging from 2 to 10. Since first presented, the Gleason score has been revised several times. In 2005 the International Society of Urological Pathology (ISUP) introduced several changes. The existence of Gleason grade 1 in any specimen was
questioned and it was agreed that Gleason grades 1 and 2 should not be diagnosed in needle biopsies. Grade 4 criteria was also changed resulting in upgrading of many earlier Gleason grade 3 [33]. The 2005 modification of the Gleason classification caused a grade migration resulting in a more favourable outcome after radical prostatectomy when using the modified compared to the original classification [34].

The Gleason score does have limitations. For example, there is a difference in the clinical outcome of Gleason 3+4 and 4+3 although both are assigned as Gleason score 7 [35]. Furthermore, as the lowest Gleason score used clinically is 6 this may result in the assumption that the cancer is in the middle of the scale. Therefore, in 2014 the ISUP proposed to change the terminology from the Gleason scoring system to the Gleason grade groups (GGG) ranging from 1 to 5 representing Gleason score 6, 3+4, 4+3, 8 and 9-10 [36]. This simplified grading system has been shown to have more accurate grade stratification with the potential to reduce overtreatment of prostate cancer [37].

**Screening for prostate cancer**

Prostate cancer can be diagnosed at an early stage by measuring prostate specific antigen (PSA) in a blood sample. PSA based screening is associated with a 30% increase in the number of men diagnosed with prostate cancer and the proportion of men diagnosed with localised prostate cancer is significantly greater [38]. The PSA test does however have some drawbacks. Although it usually is elevated in blood sample from men with prostate cancer, other benign diseases, such as BPH, prostatitis and urinary tract infection can also cause PSA elevation [39]. Additionally, 5α-reductase inhibitors, drugs that are often used to treat BPH, can reduce PSA level in the blood [40]. Thus, the PSA test often produces false-positive results, approximately 80% of positive PSA tests are false-positive when cut-offs between 2.5 and 4.0 ng/mL are used [41]. In a longitudinal study, Holmström *et al.* showed that when using a PSA cut-off of 4.0 ng/mL the sensitivity was 44% and the specificity 92% and similarly, using a cut-off of 3.0 ng/mL the sensitivity increased to 59% and the specificity decreased to 87% [42]. Although risk of prostate cancer is low for men with PSA < 1.0 ng/mL, there is no cut-off at which a man can be guaranteed to be free from prostate cancer [43].

Screening for prostate cancer is controversial. The purpose of screening is to detect the disease at an earlier stage when it can be treated with curative intention and thus decrease prostate cancer specific mortality and morbidity. But screening also results in overdiagnosis and overtreatment which can
potentially harm the patient. It is estimated that approximately 40-50% of detected prostate cancer are overdiagnosed [44-46], often resulting in overtreatment with subsequent adverse effects such as urinary incontinence, impotence, gastrointestinal toxicity, voiding and storage urinary symptoms.

Two large randomized studies have assessed the effect of PSA based screening on prostate cancer specific mortality. The Prostate, Lung, Colorectal and ovarian (PLCO) study from the United States and the European Randomized Study of Screening for Prostate Cancer (ERSPC) from 8 countries in Europe [47, 48]. Those studies report conflicting results. The PLCO study reported no mortality benefit after 7, 10 or 13 years of follow up [47, 49]. On the other hand, did the ERSPC study show survival benefits, for men in a core age group (55-69 years) that were statistically significant after 9, 11 and 13 years of follow up. In that study, Schröder et al. showed that PSA based screening reduced the rate of death from prostate cancer by 21% after 13 years of follow up. Furthermore, to prevent one death from prostate cancer 1,410, 1,055 and 781 men needed to be screened and 48, 37 and 27 additional cases of prostate cancer would need to be detected after 9, 11 and 13 years of follow up respectively [41, 48, 50].

The Swedish part of the ERSPC study, The Göteborg Randomised Prostate Cancer Screening Trial, started in 1995. In that study 20,000 men (ages 50-64, median 56 years) living in the city of Göteborg, Sweden, were invited to participate. The men were randomized in a 1:1 ratio to PSA based screening biennial or to a control group. The results showed greater mortality benefit as compared to PLCO and ERSPC. After 14 years of follow up the prostate cancer mortality was reduced almost by half. Overall, 293 men needed to be invited for screening and 12 to be diagnosed to prevent one prostate cancer death [51].

None of the above mentioned studies found a difference in overall or all-cause mortality. This probably reflects the high rates of competing mortality in this age group. Cochrane collaboration meta-analysis of five randomized controlled trials, including PLCO and ERSPC and comprised of 341,342 men in total, reported that prostate cancer screening did not significantly decrease prostate cancer–specific mortality [38]. However, that meta-analysis has received critique for combining PLCO and ERSPC in the analyses, although they had different methodologies [52]. In the first years of PLCO trial, 40% of men in the control arm underwent PSA testing and by year six that number had risen to 52% [49]. For comparison, the contamination in the ERSPC was no more than 15% [53].
In addition to the large randomized studies mentioned above, a recent register study from Sweden compared prostate cancer specific mortality in different counties in Sweden and showed that counties with high-intensity opportunistic screening had approximately 20% lower prostate cancer-specific mortality suggesting that opportunistic PSA screening decreases prostate cancer-specific mortality [54].

In 2012 did the United States Preventive Service Task Force (USPSTF) recommend against screening for prostate cancer, regardless of age [55]. This recommendation has been criticized [52, 56, 57]. In the year after the recommendations had been issued incident diagnoses of prostate cancer decreased with 28%, diagnosis of low, intermediate and high risk cancer decreased but new diagnoses of nonlocalized disease did not change [58]. Furthermore, Jemal et al. observed a decline in PSA screening rates in the United States from 38% in 2010 to 31% in 2013 [59].

**Decision aids**

Although the most widely accepted guidelines recommend against population based screening for prostate cancer [55, 60], a man may still choose to be screened because he places a higher value on the possibility of benefit than on the known drawbacks of screening. In view of this controversy, there is consensus that men need to be well informed before they undergo a PSA test. This can be achieved by use of decision aids that provide balanced, evidence-based information on the pros and cons of screening for prostate cancer. Such decision aids have been shown to increase knowledge about prostate cancer screening [61-63], decrease participation in screening and reduce the uptake of PSA testing [63-65].

**New approaches to prostate cancer screening**

In order to reduce the number of men diagnosed with and treated for prostate cancer, that has favourable prognosis without treatment, new screening methods are urgently needed. Methods that can distinguish nonprogressive or slowly progressive disease from disease that is likely to affect quality or length of life are warranted. In recent years, new methods and screening tests have evolved.

*Magnetic resonance imaging of the prostate gland*

Magnetic resonance imaging (MRI) of the prostate gland prior to biopsy can decrease the detection of clinically insignificant cancers while improving the detection of high grade disease [66, 67]. Furthermore, the overall negative
predictive value of a negative MRI before biopsy is 82% for all cancer and 98% for prostate cancer with Gleason score ≥ 7 [68].

MRI–ultrasound fusion-targeted prostate biopsy is a new technology that combines MRI-images of the prostate with conventional ultrasonography during transrectal biopsy of the prostate. In a retrospective analysis of a prospectively acquired cohort of men presenting for prostate biopsy Meng et al. reported that, compared to standard biopsy, detected MRI-ultrasound fusion-targeted prostate biopsy fewer Gleason score 6 prostate cancer and more Gleason score ≥ 7 cancer [69]. Similarly, in a recent systematic review Valerio et al. showed that MRI-ultrasound fusion-targeted biopsies detected more clinically significant cancers compared to standard biopsies (median: 33% vs 24%) using fewer biopsy cores (median: 9 vs 37) [70]. The MRI-ultrasound fusion-targeted technique has also been shown to detect more clinically significant cancer as compared to visual targeted biopsies, in particular when smaller lesions were seen on the MRI images, but that study was underpowered [71].

If there is an ongoing suspicion of prostate cancer despite negative first-line biopsy a re-biopsy can be considered as the first transrectal prostate biopsy misses about 30% of prostate cancers [72]. In a recent study, Nelson et al. concluded that MRI guided biopsy can potentially be the strategy that offers the highest cancer detection rate in a re-biopsy setting [73].

**New biomarkers**

Currently, a PSA test is the most widely used biomarker for prostate cancer screening but it is difficult to find a cut-off value with high specificity and acceptable sensitivity. A PSA cut-off value of 5.0 ng/ml is needed to achieve a specificity of 95% but resulting in a sensitivity of merely 33% [42]. Newer biomarkers and other screening methods are evolving.

The Prostate Health Index (PHI) is a mathematical formula that predicts the probability of prostate cancer based on total PSA, free PSA and (-2) form of proPSA (p2PSA). It is a simple and inexpensive blood test that has been shown to outperform conventional PSA and free PSA measurements [74]. Measuring four kallikreins (PSA, free PSA, intact PSA and human kallikrein 2) can enhance prostate cancer detection compared to PSA and age alone [75]. The 4Kscore is a combination of measurement of the above mentioned four kallikreins in blood and clinical information (age, digital rectal examination of the prostate and history of prior prostate biopsy) that estimates the probability of significant prostate cancer. It can reduce number of biopsies with 30-58% with delayed diagnosis in only 1-5% of significant cancer [76].
In the Stockholm 3 (STHLM3) model a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, human kallikrein 2, β-microseminoprotein (MSMB) and macrophage inhibitory cytokine 1 (MIC1)) genetic polymorphism (232 single nucleotide polymorphisms (SNPs)), clinical variables (age, family history, previous prostate biopsy and prostate examination) and PSA concentration are measured to calculate the probability of prostate cancer. The STHLM3 model performed significantly better than PSA alone for detection of Gleason score ≥ 7 prostate cancer and could reduce the number of prostate biopsies by 32% and avoid 44% of benign biopsies [77].

**Curative treatment of prostate cancer**

Men who are diagnosed with localised prostate cancer are often offered curative treatment. Common radical treatments for localised prostate cancer include radical prostatectomy, external beam radiotherapy and brachytherapy. Newer, less invasive treatment alternatives are evolving, for example cryotherapy and high-intensity focused ultrasound (HIFU).

Since the beginning of the PSA era, more men are diagnosed with low-grade prostate cancer. Although low-grade cancer can become more aggressive over time it is usually clinically insignificant and the possible benefits of curative treatment need to be balanced against the risk of adverse effects associated with radical treatment. Consequently, active surveillance can be a suitable treatment alternative for men with low-grade cancer and should be recommended as a first-line treatment to carefully selected patients.

**Radical prostatectomy**

Surgical treatment for prostate cancer started in the beginning of the 20th century. On April 7, 1904 the urologist Hugh Hampton Young performed the first radical prostatectomy, using perineal approach and in 1945 Terence Millin performed the first retropubic radical prostatectomy. A significant development of the surgical technique came in 1983 when Patrick Craig Walsh described the anatomical basis of the surgery and how adverse effects could be avoided [78]. The first successful laparoscopic radical prostatectomy was performed by Schuessler in 1991 but the technique never gained widespread acceptance because of technical difficulty, long learning curve and limited advantage over the standard retropubic radical prostatectomy [79]. The next significant advance in the surgical treatment of prostate cancer came when the first reported robot-assisted radical
prostatectomy was performed in 2001 and has since then gained widespread acceptance worldwide [80].

Comparison of surgical approaches
The different surgical approaches to radical prostatectomy have been compared in a number of studies. The retropubic and robot-assisted radical prostatectomies have similar oncologic outcome in recent systematic reviews and meta-analyses [81, 82]. Furthermore, the 90-day postoperative mortality is low and comparable between the surgical techniques [83]. However, the surgical techniques differ in pattern of adverse effects after surgery. Although most studies have shown similar risk of urinary incontinence and erectile dysfunction [84, 85], recent systematic reviews showed that robot-assisted radical prostatectomy did have lower risk for that adverse effects [86-88]. Minimally invasive surgeries usually have lower risk for post-operative infection and bleeding and this is also true for robot-assisted radical prostatectomy [89-92]. Risk of thromboembolic disease is lower after the robot-assisted technique and the post-operative hospital stay is shorter [93, 94]. On the other hand does the conventional retropubic radical prostatectomy have advantages regarding operating time, cost and possibly risk of post-operative small bowel obstruction [92, 95, 96].

Inguinal and incisional hernia are known adverse effects after radical prostatectomy. There is conflicting data on whether risk of inguinal hernia is higher after robot-assisted or retropubic radical prostatectomy [97, 98]. In a study using data from the Surveillance, Epidemiology, and End Results Program (SEER) database risk of incisional hernia was more than 3-fold higher after robot-assisted radical prostatectomy [99].

Little is known about long-term risk of lower urinary tract symptoms (LUTS) after radical prostatectomy. In a recent paper from the SEER database was the occurrence of urinary adverse effects after radical prostatectomy approximately 27% and in a study from the Cancer of the Prostate Strategic Urologic Research Endeavor registry (CaPSURE) was the rate of urethral stricture after surgery 8% [100, 101]. Furthermore, the incidence of urethral stricture and urinary retention has been found to be lower after robot-assisted radical prostatectomy [102].

Survival benefit of surgery
In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) radical prostatectomy was compared with watchful waiting. The primary end points were overall mortality, prostate cancer-specific mortality and risk of metastases. The results showed that radical prostatectomy decreased overall and prostate cancer-specific mortality and the number needed to treat to
prevent one death was 8. Furthermore, radical prostatectomy was associated with reduced risk of metastases among older men [103]. By contrast, at a median follow-up of 10 years, the Prostate Cancer Intervention versus Observation Trial (PIVOT) only suggested a modest survival benefit among a subgroup of men with a PSA value greater than 10 ng/mL and/or an intermediate risk prostate cancer. As in the SPCG-4 showed PIVOT that men who underwent radical prostatectomy had lower risk of bone metastases [104]. A possible explanation for the difference in the results from SPCG-4 and PIVOT is that men included in PIVOT did generally have low-risk prostate cancer. Current data suggest that men with low-risk prostate cancer treated with active surveillance have comparable prognosis as men treated with radical treatment [105-107].

**Radiotherapy**

Radiotherapy for prostate cancer has almost as long a history as surgical treatment. Initially, radium was inserted into the prostate with specially designed applicators. This treatment was later known as brachytherapy. Further improvements in brachytherapy came in 1951 when Flocks et al. injected radioactive gold into the prostate cancer [108]. Few decades later, the external beam radiotherapy evolved and significant improvement of the technique came in the beginning of the 21st century.

*External beam radiotherapy*

External beam radiotherapy (EBRT) involves the use of ionizing radiation from either x-rays or proton beams to kill malignant cancer cells. Before the CT-era, exactly locating the prostate before treatment was difficult. Thus, the rectum, bladder and other adjacent organs received relatively high radiation doses resulting in adverse effects from the gastrointestinal tract and genitourinary system. In the 1990s began the era of three-dimensional visualization and treatment planning using CT-scans. This allowed higher radiation doses to be aimed with more precision to the prostate while minimising the dose to the surrounding normal tissues. This is described as three-dimensional conformal radiation therapy because the radiation beams conform to the shape of the treatment target.

One of the goals of improving radiation techniques is to increase the dose received by the target organ while simultaneously minimising the radiation dose to adjacent organs. A major advance in the delivery of radiation came with the advent of intensity-modulated radiation therapy (IMRT). By using advanced software and hardware adaptions to linear accelerators the intensity of radiation can be varied from each beam angle. This approach
results in lowering of radiation doses to the rectum, bladder, femoral heads and small bowel [2].

It has been reported that radiotherapy prolongs overall survival as compared to endocrine therapy alone. In a study from Scandinavia, 875 men with high- or intermediate-risk prostate cancer were randomized to endocrine therapy alone or in a combination with radiotherapy. The final results from the study showed that prostate cancer-specific mortality was 34% for men receiving endocrine therapy only and 17% in the group that received combination treatment. Furthermore, was the median overall survival prolonged by 2.4 years in the arm receiving both radiation and endocrine treatment [109].

**Brachytherapy**

Brachytherapy for prostate cancer, also known as ‘seed implant’, involves the insertion of permanent radioactive source directly into the prostate. These sources or ‘seeds’ give off a localised radiation that penetrates few millimetres into the adjacent tissue. For treatment of the whole prostate, multiple ‘seeds’ must be implanted with millimetre precision. The ‘seeds’ are usually inserted into the prostate transperineally with the aid of transrectal ultrasonography and a template with a pattern of parallel holes. Brachytherapy can be used as a monotherapy or in a combination with external-beam radiotherapy [2].

**Outcome after radical treatments for prostate cancer**

The overall and prostate cancer-specific survival is similar after radiotherapy and radical prostatectomy. In the Prostate Testing for Cancer and Treatment (ProtecT) trial 1,643 men with clinically localized prostate cancer, mostly T1c and Gleason 6, were randomized to radical prostatectomy, radiotherapy or active surveillance [110]. The study showed no significant difference in prostate cancer-specific mortality between the treatment groups but risk of disease progression and metastases was higher among men in the active surveillance group. In contrast to the SPCG-4 and PIVOT studies, men in the active surveillance group were offered radical treatment in case of disease progression. Within 3 years after their initial assignment had a quarter of them received radical treatment and over half by 10 years but 44% of the men did not receive radical treatment and thus avoided adverse effects [107].

**High-intensity focused ultrasound (HIFU)**

A relatively new medical device, high-intensity focused ultrasound (HIFU), has some appealing features. It is technically relatively simple. A specific HIFU probe that generates ultrasound waves is inserted transrectally and
the prostate tissue is thermally ablated with the instrument. HIFU may be used for focal therapy or total prostate ablation.

HIFU ablation of the whole prostate gland has been shown to have acceptable oncological medium-term outcome with a low risk of urinary incontinence and a similar risk of erectile dysfunction as other radical treatments. In a recently published paper, Dickinson et al. reported that at five years after treatment was the overall survival 95%, prostate cancer-specific survival 98% and failure-free survival 70%. Furthermore, 88% of the men that were pad-free before the HIFU treatment remained pad-free after treatment and of the men with good baseline erectile function 39% preserved their erectile function [111].

Prostate cancer is most often a multifocal disease [112]. Thus, radical treatment of the whole prostate gland is a standard treatment of localised cancer. Focal therapy is emerging as an alternative in the management of selected patients. The aim is to achieve a good long-term control of the cancer with fewer adverse effects than radical treatment. Focal therapy may even postpone radical treatment and thus, delay eventual bothersome adverse effects.

Approximately 20% of men with prostate cancer have unilateral disease that can be treated with HIFU-hemiablation. A recent report from France showed promising results with approximately 95% of the treated men without clinically significant cancer in the treated lobe at control biopsy one year after treatment. Furthermore, the adverse effects of the treatment were few, 97% of the men had preserved urinary continence and 78% preserved their erectile function [113]. In another study from Belgium the outcome after hemiablation with HIFU was compared with RARP. At 36 months median follow-up was HIFU associated with better and faster recovery of urinary continence and lower risk of de novo erectile dysfunction. No statistically significant difference was found between the treatments regarding the need of salvage radiotherapy but 7/55 men needed a complementary HIFU treatment of the contralateral lobe [114].

**Cryotherapy**

Cryotherapy uses a concept that is similar to HIFU to treat prostate cancer with focal therapy of tumor in the prostate or the whole gland. With transrectal ultrasound guidance, 12 cryoablation needles are inserted into the prostate transperineally. Pressurized argon gas is then used to cool the tissue below -40°C that causes tumor cell lysis. An ice ball forms in the tissue and its expansion is monitored with transrectal ultrasonography. Two cycles
of freezing and thawing results in more extensive tissue damage and better cancer control than a single cycle treatment. Systematic temperature monitoring devices and a warming Foley catheter protects the urethra from damage and minimizes adverse effects after treatment.

The advantage of cryotherapy is easy accessibility via transperineal needles to all parts of the prostate, including the anterior part. The procedure is minimally invasive and can be repeated. However, the procedure can cause damage to adjacent tissues particularly when treating tumors close to the prostate capsule or the urinary sphincter muscle. This results in erectile dysfunction rates of 15-40% and incontinence rates of 1-10% following focal therapy [115].

Both focal and whole-gland cryoablation has been reported to be effective and save. However, there is conflicting data on oncological outcome and rate of adverse effects as compared to radical treatments, such as radiotherapy and radical prostatectomy [116-118].

**Active surveillance**

Active surveillance is a conservative treatment for men with low-grade prostate cancer that allows delayed primary treatment. For these men, surveillance is thought to avoid unnecessary treatment and risk of associated adverse effects. With signs of progression of the cancer, such as increase in PSA or progression on repeat biopsies, radical treatment is usually recommended. Active surveillance is distinct from watchful waiting which refers to monitoring the patient until he develops metastases that require androgen deprivation therapy.

As a result of widespread screening for prostate cancer a large number of men are diagnosed with clinically insignificant prostate cancer. This overdiagnosis often results in overtreatment and adverse effects to treatment. To minimize overtreatment, men with low-grade prostate cancer can be offered active surveillance without affecting the prostate cancer-specific mortality but lowering the risk of adverse effects.

In the ProtecT trial functional and oncological outcomes after radical prostatectomy, radiotherapy and active surveillance were compared. The study results have recently been published and showed that for men with localized prostate cancer, active surveillance had comparable oncological outcome and lower risk of adverse effects as compared to radiotherapy and radical prostatectomy. However, of the 1,643 men who underwent randomization, only 17 prostate cancer-specific mortalities were reported
after 10 year follow-up, 8, 5 and 4 after active surveillance, radical prostatectomy and radiotherapy respectively [107, 119].

The Prostate Cancer Research International: Active Surveillance (PRIAS) study offers active surveillance protocol to urologists worldwide via web-based instrument. As of July 2011, 2,079 were included in PRIAS. In a recent study from PRIAS, Bul et al. reported that men who were initially followed with active surveillance but received deferred radical prostatectomy had organ-defined disease and favourable Gleason grading in majority of cases [120].

The Göteborg Randomised Prostate Cancer Screening Trial is part of the ERSPC study mentioned earlier. In the Göteborg study, men diagnosed with very low-, low- or intermediate risk prostate cancer were managed with active surveillance. These men underwent PSA tests every 3-12 months and rebiopsies in cases of clinical progress. Men with stable disease underwent rebiopsies every 2-3 year. Triggers for intervention were disease progression or patient initiative. After median follow-up of eight years 43% of the men discontinued active surveillance and initiated treatment. The authors concluded that active surveillance is a safe alternative for men with very low-risk cancer [105].

In a single center, prospective cohort study from Canada, long-term outcome for active surveillance was assessed. In total, 993 patients were included and after a median of 6.4 year follow-up, 15 deaths (1.5%) from prostate cancer were registered. The 10- and 15-year prostate cancer-specific survival was 98% and 94% respectively. At 15 year, 55% of the patients remained untreated and on surveillance [106]. Similarly, another single center study from the United States showed that prostate cancer-specific and metastasis-free survival rates were approximately 100% at 10 and 15 years for men in a prospective active surveillance program [121]. This indicates that for favourable-risk localized prostate cancer is active surveillance feasible and safe.

**Adverse effects to diagnosis**

Prostate cancer is usually diagnosed with transrectal ultrasound guided biopsy. The procedure is considered safe but most men experience it as uncomfortable or painful. It is associated with adverse effects, such as hematochezia, hematuria and hematospermia [122]. Severe adverse effects are rare but despite use of prophylactic antibiotics febrile urinary tract infection and urosepsis have been reported in 1-4% of biopsied men and
hospital admissions for those adverse effects have been increasing in the United States, Canada and Europe [123-125].

In a study from PCBaSe, Lundström et al. assessed the frequency of urinary tract infection and hospital admission by using data from the Prescribed Drug Register and the National Patient Register. The results showed that within one month from biopsy, 6% of the men had dispensed prescription for urinary tract antibiotics and 1% were hospitalised for an infectious complication [126].

The 30-day mortality after transrectal prostate biopsy is low. Nam et al. estimated the 30-day mortality rate to approximately 0.1%[125] but studies from the United States and Europe did not show any increase in mortality rate within 30-days after biopsy [123, 124].

**Adverse effects to curative treatment**

Curative treatments for prostate cancer are associated with substantial risk of adverse effects but the risk is different between treatment alternatives. Radical prostatectomy is associated with higher risk of urinary incontinence and erectile dysfunction but radiotherapy is associated with higher risk of bowel disturbances and irritative urinary symptoms [119]. Table 1 lists the most common adverse effects after radical prostatectomy and curative radiotherapy. The definitions of adverse effects are inconsistent in the literature causing a wide range of the proportion of men that suffer from a particular adverse effect.

In a report from the Prostate Cancer Outcome Study (PCOS), urinary incontinence and erectile dysfunction were more common after radical prostatectomy than after radiotherapy, whereas bowel symptoms were more frequent after radiotherapy. However, at 15 years after treatment was the risk similar after radical prostatectomy and radiotherapy [127]. In a questionnaire study from the NPCR 14% of men reported moderate and 10% severe urinary incontinence after radical prostatectomy [128]. In another study from the NPCR, 87% reported erectile dysfunction or sexual inactivity, 20% urinary incontinence and 14% bowel disturbances at 12 years after treatment for prostate cancer. As compared to controls was the risk of urinary incontinence increased after radical prostatectomy but not after radiotherapy but the opposite was true for bowel disturbances. Furthermore, risk of urinary urgency was increased after radiotherapy but radical prostatectomy was associated with significantly lower risk of urinary urgency [129]. For men that receive radical prostatectomy, nerve sparing technique is associated with better outcome on sexual quality of life [130].
Table 1. Most common adverse effects after radical prostatectomy and radiotherapy [16]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse effect</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical prostatectomy</strong></td>
<td>Erectile dysfunction</td>
<td>20-100%</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>Any 0-70%; severe 0-4%</td>
</tr>
<tr>
<td></td>
<td>Urethral stricture</td>
<td>0-12%</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td>Gastrointestinal</td>
<td>Any 2-100%; severe 0-20%</td>
</tr>
<tr>
<td></td>
<td>Genitourinary</td>
<td>Any 0-70%; severe 0-20%</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>Any 0-60%; severe 2-15%</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td>10-85%</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

The size of the prostate does have different effect on the functional outcome after radical prostatectomy and radiotherapy. Large prostate size exerbes urinary irritation after radiotherapy whereas after radical prostatectomy, large prostate size at baseline is associated with improvement in urinary irritation [107].

The prostate cancer-specific survival is comparable after radical prostatectomy and radiotherapy but the pattern of adverse effects is different [107]. Studies on health-related quality of life after treatment for prostate cancer have shown that the available treatments have negative effect on quality of life and increases anxiety among the patients [119, 131]. Thus, it is paramount to carefully select the most appropriate treatment for the individual patient. Patient preferences and baseline factors, such as age, prostate size and LUTS, need to be evaluated in order to give appropriate clinical recommendations regarding treatment selection.
Aims of this thesis

The overall aims of this thesis were to compare different treatment alternatives for localized prostate cancer with respect to risk of rehospitalisation and adverse effects.

Specific aims were to study:

- The adherence to National Guidelines on informing asymptomatic men about the pros and cons of screening for prostate cancer with PSA and which type of information they received.

- The frequency of rehospitalisation within 90 days after radical prostatectomy and to assess if there was a difference between retropubic and robot-assisted radical prostatectomy.

- The risk of long-term adverse effects after radiotherapy and radical prostatectomy as compared to prostate cancer-free background population and compare the risk between the two treatments.

- The risk of adverse effects after radical prostatectomy and compare the risk between retropubic and robot-assisted radical prostatectomy.
Materials and methods

Data sources

The National Prostate Cancer Register (NPCR)

In the 1980s and 1990s was a rapid increase in the incidence of prostate cancer in Sweden, probably a result of the introduction of PSA testing. Diagnostic methods and treatment for prostate cancer varied in different parts of Sweden and it was considered vital to collect data for more detailed analyses of the characteristics, treatment and outcome of prostate cancer. This stimulated Swedish urologists to create the National Prostate Cancer Register (NPCR) that started in 1987 in the south-east healthcare region of Sweden and became nationwide in 1998 [132]. Since 1998, the NPCR captures approximately 98% of all prostate cancer cases as compared to the Swedish Cancer Register to which registration is mandated by law [133]. The Swedish Cancer Register has high overall completeness and captures virtually all prostate cancer cases [134]. The NPCR includes data on tumor stage, tumor differentiation, serum level of PSA, work-up and primary treatment. Since 2008 patient reported outcome measures (PROM) and patient reported experience measures (PREM) are registered [135]. The quality of data registered in NPCR is good with a mean value of 90% completeness for the registered variables [136].

The Prostate Cancer data Base Sweden (PCBaSe)

In 2008, NPCR was linked to a number of other Swedish population-based registers to create a large nationwide, population-based database called Prostate Cancer data Base Sweden (PCBaSe) [128, 137]. This was possible by using the unique, Swedish personal identity number [138]. For each case included in the PCBaSe, five prostate cancer-free men in the background population, matched by year of birth and county of residence, were randomly selected and included in the database as controls. In 2012 the PCBaSe 3.0 included data on 149,770 cases from up to 11 national registers (figure 3).
The National Patient Register

As of 1987, the National Patient Register is a nationwide register that collects information on in-patient and out-patient care. Each medical record contains information on discharge diagnoses, coded according to the International Classification of Diseases (ICD 9 or 10) and interventions, coded according to the Nordic Medico-Statistical Committee (NOMESCO) classification of surgical procedures. The National Patient Register captures almost all in-patient episodes and the positive predictive value of diagnoses in the In-patient Register is 85-95% but the capture of out-patient care is lower or approximately 80% [139]. To assess the burden of concomitant diseases, Charlson Comorbidity Index (CCI) was calculated, based on data in the National Patient Register as previously described [140, 141]. The CCI is an index that consists of 18 groups of diseases with a specific weight assigned to each disease category (1, 2, 3 and 6). The weights are then summed to obtain an overall score, resulting in the three comorbidity levels of the index: 0 for no comorbidity, 1 for mild, 2 for moderate and ≥ 3 for severe comorbidity [128].

LISA database

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by its Swedish acronym) holds annual registers since 1990 and includes all individuals registered in Sweden that are aged ≥ 16 years. The database includes data on socioeconomic factors such as marital
status and educational level [142]. The levels of education used in the current thesis were low (compulsory school ≤ 9 years), medium (high school = 10-12 years) and high (college or university > 12 years).

RetroRad

There is little information regarding radiotherapy in the National Patient Register but since 2008 the NPCR collects information on type of radiotherapy. To accommodate the lack of information prior to 2008 a retrospective data collection was performed and registered in RetroRad. Information on type of radiotherapy, treatment time, total dose and fractionation was retrieved directly from radiotherapy verification/oncology information systems and local databases in oncology departments in Sweden. RetroRad captures information from early 1990s until 2008-12, depending on the availability of databases at each centre [143].

Tumor risk category in NPCR

Based on tumor stadium, Gleason score and PSA level the prostate cancer was classified into different risk categories in a modification of the National Comprehensive Cancer Network (NCCN) categorisation (table 2). Men with stage T4, N1 or M1 or PSA ≥ 50 ng/mL were excluded from the analyses.

<table>
<thead>
<tr>
<th>Tumor risk category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>T1-2, Gleason score ≤ 6 and PSA ≤ 10 ng/mL</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>T1-2, Gleason score = 7 and/or PSA 10 to &lt; 20 ng/mL</td>
</tr>
<tr>
<td>Localized high risk</td>
<td>T1-2, and/or Gleason score 8-10 and/or PSA 20 to &lt; 50 ng/mL</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>T3, and PSA &lt; 50 ng/mL</td>
</tr>
</tbody>
</table>

Table 2. Classification of tumor risk category of prostate cancer
Study design, selection of cases and statistical methods

*Paper I*

In this cross-sectional study, the NPCR was used to select the cases. Between 2006 and 2008, 600 asymptomatic men diagnosed with T1c prostate cancer were annually selected so that the study population consisted of 1,800 cases. All of the included men had been diagnosed with prostate cancer as a part of health examination that included a PSA test.

In 2007, the National Board of Health and Welfare issued National Guidelines, recommending that men considering PSA testing should receive written information on the pros and cons of the PSA test. To assess the impact of those guidelines, the study period was selected so that it covered the last year before and the first year after the guidelines were issued.

The total number of prostate cancer cases registered in the NPCR was 9,111 in 2006, 8,853 in 2007 and 8,788 in 2008 [144]. The mean age of the men was 64.2 years (range 40-88 years). In a questionnaire, sent out by ordinary mail, these randomly selected men with screening-detected prostate cancer were asked if and how they had been informed about the pros and cons of PSA based screening for prostate cancer. The questionnaire was sent out 2-3 years after the diagnosis of prostate cancer. A reminder was sent to non-responders 2-3 months after the first letter. The survey questionnaire is presented in figure 4.

The survey questionnaire was only sent to men that subsequent to the PSA test were diagnosed with prostate cancer but not to men in the general population who had undergone PSA testing. This might have caused a selection bias. Alternatively, the survey questionnaire could have been sent to randomly selected men in the background population who had recently had a PSA test. However, information on which men were asymptomatic at the time of PSA testing is only registered in the NPCR. Hence, it is difficult if not impossible to identify which prostate cancer-free men in the general population were asymptomatic at the time of PSA testing. As the main purpose of the study was to assess the proportion of informed men who underwent screening for prostate cancer, this information was necessary. Furthermore, we have no reason to believe that prostate cancer-free men have received the information in any other way and the results are therefore likely representative for all men in Sweden.
Questionnaire concerning information on PSA testing

1. What was the reason for your first PSA-test?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>I had voiding symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had other symptoms from the urine or genital organs (ex. pain, blood in semen, blood in urine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I was worried about having prostate cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I was worried about having prostate cancer as I have relatives diagnosed with prostate cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My wife/girlfriend/partner urged me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My doctor recommended that I should have the PSA-test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One discusses and reads about it in the media that “you should check your PSA”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had sought medical care for something else</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had a regular health examination</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. What information did you receive before the PSA-test?

- Oral information on the pros and cons of PSA-testing
- Written information on the pros and cons of PSA-testing
- Oral and written information on the pros and cons of PSA-testing
- No information on the pros and cons of PSA-testing
- No information on that the PSA-test had been taken

3. Did the information on the pros and cons of PSA-testing influence your decision on having the test?

- Yes
- No
- Received no information on the pros and cons of PSA-testing

4. How did you receive information on the result from the PSA-test?

- by a letter
- With telephone call
- at an appointment with my physician
- I was not informed on the PSA-value

I have read the enclosed written information and I agree to participate in the study and that my personal information will be treated as described.

Place and Date

Signature___________________ Clarification of Signature___________________

Thank you for your participation!

Figure 4. The questionnaire used in paper 1.
In this register-based cohort study all men that were registered in PCBaSe and underwent radical prostatectomy in Sweden between 2000 and 2011 were included. Date of surgery and rehospitalisation was retrieved from the National Patient Register. Risk of rehospitalisation within 90 days was assessed and compared between retropubic radical prostatectomy (RRP), laparoscopic radical prostatectomy (LRP) and robot-assisted radical prostatectomy (RARP). Furthermore, by using data on discharge diagnoses and surgical procedures, registered in the National Patient Register, the cause of rehospitalisation was analysed. Discharge diagnoses were classified into five groups (table 3) where the first three groups were regarded as adverse effects to surgery and other groups as medical conditions.

**Table 3.** Main indications for readmission

<table>
<thead>
<tr>
<th>Main indications for readmission</th>
<th>Most common diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical</strong></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Haemorrhage, haematuria, anaemia</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection following procedure, urinary tract infection, sepsis</td>
</tr>
<tr>
<td>Other</td>
<td>Urinary retention, abdominal pain, bladder neck obstruction</td>
</tr>
<tr>
<td><strong>Serious medical conditions</strong></td>
<td>Pulmonary embolism, atrial fibrillation, myocardial infarction</td>
</tr>
<tr>
<td><strong>Other medical diagnoses</strong></td>
<td>Disease of musculoskeletal system, mental disorders</td>
</tr>
</tbody>
</table>

The surgical procedures were classified as related or not related to adverse effects to surgery. Surgical procedures that were related to adverse effects after surgery were further divided into transurethral procedures, procedures performed with local anaesthesia and procedures performed with general anaesthesia (table 4).

**Table 4.** Main interventions at rehospitalisation. PCI = percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>Related to adverse effects</th>
<th>Most common interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Related to adverse effects</strong></td>
<td></td>
</tr>
<tr>
<td>Transurethral</td>
<td>Cystoscopy, transurethral resection of bladder neck, urethrotomy</td>
</tr>
<tr>
<td>With local anaesthesia</td>
<td>Catheterization of bladder, percutaneous puncture of bladder</td>
</tr>
<tr>
<td>With general anaesthesia</td>
<td>Laparotomy, vacuum treatment of wound, repair of dehiscence</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>PCI, gastroscopy, coronary bypass surgery</td>
</tr>
</tbody>
</table>

Readmission rate was used as a quality indicator of total perioperative care. The advantage of readmission rate is that it is an easy and reliably measure to use in a register-based study. Virtually all admissions to a hospital in Sweden are registered in the National Patient Register.
rate a robust measure of perioperative quality. The main drawback is that the reason for readmission is not assessed. This might cause bias as although the different study cohorts had similar readmission rates the different surgical methods might differ in the severity of adverse effects leading to readmission. To overcome this problem, a subgroup analysis was performed analysing the discharge diagnoses and surgical interventions at readmission.

By using 90-day readmission rate most short-term adverse effects leading to admission were captured but some common long-term adverse effects, such as obstructive LUTS, were likely missed. With longer follow-up, more adverse effects had been captured, but the number of men admitted for other reason than adverse effects after radical prostatectomy would also increase. On the other hand, shorter follow-up, would likely have decreased the capture of adverse effects.

The problem with overestimation of readmission, caused by admissions unrelated to radical prostatectomy, could have been overcome by analysing the readmission rates in the study cohorts compared to admission rates for prostate cancer-free controls from the background population. Each control could have been given a date for pseudo-surgery and the 90-day admission rate analysed. Unfortunately, when the analyses in paper II were performed, no control group was available in the PCBaSe and it would have been techniqually difficult, if not impossible to include a reliable control group in the analyses at that time. However, the proportion of men admitted for other reasons than adverse effects after radical prostatectomy is likely similar in the study cohorts and therefore the results from the main analyses are probably not affected.

Data on many known or suspected confounders could be retrieved from different quality registries included in PCBaSe. For the statistical analyses, multivariable logistic regression was used to calculate the odds ratio (OR) as a measure of risk of 90-day rehospitalisation, considering surgical method, calendar period, patient age, tumor risk category, perioperative hospital stay, CCI, education level and hospital surgical volume.

As the study included virtually all men in Sweden that underwent radical prostatectomy during the study period the results are representative for all men in Sweden and data are likely reproducible for men in other countries with similar population and clinical practices regarding radical prostatectomy.
**Paper III and IV**

In these register-based cohort studies, men registered in PCBaSe and underwent radiotherapy (RT) with curative intention or radical prostatectomy (RP) were included in the study as cases. For each case five prostate cancer-free men, matched for birth year and county of residence, were randomly selected from the background population and included in the study as controls. Men with stage T4, N1 or M1 or PSA ≥ 50 ng/mL at diagnosis were excluded and men that received salvage RT or RP were excluded at the date of secondary treatment. In paper III, the intermediate- and localized high tumor risk groups were merged into one group.

From 1997 have the registries mainly used in the paper III, NPCR and RetroRad, high coverage. Therefore, the selected study period was between 1997 and 2012. Before 2004, very few RARPs were performed in Sweden. Thus, the study period in paper IV was between 2004 and 2014.

Adverse effects of RT and RP were assessed by using diagnostic and intervention codes registered in the National Patient Register after treatment. In paper III the diagnostic codes were classified into four domains and the surgical procedures were also classified into four different domains (table 5).

**Table 5.** Domains of adverse effects and surgical procedures. GI = gastrointestinal.

<table>
<thead>
<tr>
<th>Domain of adverse effects</th>
<th>Most common diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td>Stress incontinence, other specified urinary incontinence</td>
</tr>
<tr>
<td>Storage LUTS</td>
<td>Cystitis, neuromuscular dysfunction of bladder</td>
</tr>
<tr>
<td>Obstructive LUTS</td>
<td>Bladder neck obstruction, urethral stricture</td>
</tr>
<tr>
<td>GI-diagnoses</td>
<td>Haemorrhoids, noninfective enteritis and colitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain of surgical procedures</th>
<th>Most common procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td>Artificial sphincter, paraurethral injection</td>
</tr>
<tr>
<td>Lower urinary tract</td>
<td>Cystoscopy, bladder catheterization</td>
</tr>
<tr>
<td>Upper urinary tract and reoperations</td>
<td>Insertion of stent into ureter, nephropyelostomi</td>
</tr>
<tr>
<td>GI-tract and abdominal wall</td>
<td>Colonoscopy, proctoscopy, sigmoidoscopy</td>
</tr>
</tbody>
</table>

In paper IV the adverse effects after surgery were compared between RARP and RRP. The analysed diagnoses were similar to the codes analysed in paper III but diagnoses of hernia were analysed but not diagnoses of gastrointestinal adverse effects. A complete list of analysed diagnostic and surgical codes is presented in table 6.
Table 6. Domains of adverse effects and surgical procedures. GI = gastrointestinal.

<table>
<thead>
<tr>
<th>Domain of adverse effects</th>
<th>Most common diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td>Stress incontinence, other specified urinary incontinence</td>
</tr>
<tr>
<td>Obstructive LUTS</td>
<td>Bladder neck obstruction, urethral stricture, urinary retention</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>Inguinal hernia</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>Incisional hernia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain of surgical procedures</th>
<th>Most common procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td>Artificial urinary sphincter, paraurethral injection</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>Repair of inguinal hernia</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>Repair of incisional hernia</td>
</tr>
<tr>
<td>Obstructive LUTS</td>
<td>Bladder neck incision or resection, catheterisation of bladder</td>
</tr>
<tr>
<td>Urethroscopy</td>
<td>Cystoscopy, urethroscopy</td>
</tr>
</tbody>
</table>

In both paper III and IV, number of events were assessed instead of assessing the number of men that suffered from an adverse effect. Each man could therefore have more than one event registered. As more events can be an indication of more severe adverse effects, using number of events gives additional information compared to analysing only number of men suffering from the analysed adverse effects. However, a second identical diagnosis or procedure was ignored within 2 months after the first event. This was done because the same event can be registered more than once in the National Patient Register, for example both in the In-patient Register at admission to hospital and in the Out-patient Register at a follow-up visit after discharge from the hospital. This time interval was also excluded from the time at risk in the analyses.

In the first steps of RARP, the abdominal wall is usually incised above or below the umbilicus to gain intra-abdominal access for the camera used during the surgery. At the end of surgery, this defect of the abdominal wall is sutured. Incisional hernias in this defect can be misclassified as umbilical hernia because of the proximity to the umbilicus. In fact, 10 years before surgery 0.8% and 0.7% of the men were diagnosed with umbilical hernia but 10 years after surgery 0.7% and 1.2% of the men were diagnosed with umbilical hernia after RRP and RARP respectively. Thus, the frequency of umbilical hernia remained stable after RRP but increased by approximately 70% after RARP. This might suggest that incisional hernia is often misclassified as umbilical hernia after RARP. However, as it is impossible to know which men eventually received wrong diagnosis, further analyses of this subject could not be performed.

The statistical analyses were similar in paper III and IV. In paper III, the main analyses focused on men with intermediate and localised high-risk
prostate cancer as this was the most balanced group in terms of proportion of men who underwent RT or RP.

Incidence rate ratios (IRRs) of the selected diagnoses and procedures for each study cohort were calculated for each 3 year interval up to 12 and 10 years after primary treatment in papers III and IV respectively. The controls did not affect the results in paper IV and were therefore omitted. On the other hand did the controls influence the results in paper III and the IRRs were used in subsequent analyses. The treatments were compared, RT vs RP in paper III and RARP vs RRP in paper IV. This was done by using multivariable Poisson regression analysis for the analysed adverse effects. In paper III we adjusted for treatment year, age, CCI, educational level, PSA level, clinical T-stage and biopsy Gleason score. In paper IV hospital surgical volume was also a confounder that was adjusted for in the analyses. Hospital surgery volume was defined as high > 100 RPs/year, intermediate = 50-99 RPs/year or low < 50 RPs/year.
Ethical considerations

The studies in this thesis are based on data from the PCBaSe. No other data was collected from the study subjects except for paper I, where all responders provided a completed questionnaire that can also be considered as an informed consent to participate.

None of the subjects were contacted in person and thus could not be harmed physically. The subjects were in a small risk for breach of confidentiality, which should be balanced against the potential value of new knowledge from these studies. Studies on cancer epidemiology are generally accepted by society as they can result in better health and quality of life for those diagnosed with cancer. The small risk of breach of confidentiality was minimized by using strict protection and data security in all steps of our studies. This included an exchange of the personal identity number to a study number and no study file included the person identity number. The key to the person identity number was held at The Board of Health and Welfare. All statistical analyses were performed using the Research Portal, a secure server that enables statisticians to work with data from registries on their own computers without the risk of the data being lost or altered. Results were presented at an aggregate level in tables and figures.

In January 2012 the European Commission suggested that processing of data for scientific reason should not be exempt from strict requirements of specific consent by research participants [145]. This would have severely restricted European epidemiological research [146]. On 15 December 2015, the European Parliament, the Council and the Commission reached agreement on the new data protection rules. The Regulation entered into force on 24 May 2016 and applies from 25 May 2018. Using personal data in research will still be permitted. However, it is difficult to predict how the new regulation will impact epidemiologic studies based on data from national registries.

In large-scale epidemiological research collection of informed consent is unfeasible. Men registered in NPCR have not signed an informed consent for participation but can decline participation in the register. In all centres that report data to NPCR information on this possibility, the so-called opt-out principle, is provided to the patients, usually by posting that information on a clearly visible place at the treating clinic. This information is also available at the www.npcr.se web site.

The Research Ethics Review Board at Umeå University Hospital has approved the PCBaSe project multiple times and the most current version,
PCBaSe 3.0 was approved in 2013, UmU Dnr 2013-53-3. All studies included in this thesis were approved by the Research Ethics Review Board at Umeå University Hospital. For paper III and IV a specific amendment was submitted and approved.
Results

Paper I

Of the 1,800 men invited to participate in the study 1,621 (90%) responded. Approximately 63% of the responders reported that they had received information on PSA test prior to blood draw, 27% had not received any information and 10% were not aware of that they had undergone a PSA test.

There was little difference in the proportion of informed men during the study period (figure 5). In total, 49% had received oral information only, 12% received both oral and written information and 3% received only written information. There was a small increase in the proportion of men that received written or both oral and written information, from 12% in 2007 to 16% in 2008.

Figure 5. Proportion of the information received prior to PSA test during the study period.
**Paper II**

In the study period between 2000 and 2011 there were 24,122 registered RPs in PCBaSe that could be further analysed. Specifically, 16,375 RRP, 1,354 LRP and 6,393 RARP were performed during the study period. Compared to men that underwent RRP, men treated with LRP and RARP were more often younger than 60 years, had a lower tumor risk category, higher educational level and a shorter perioperative stay.

The frequency of readmissions within 90 days postoperatively was approximately 10%. In total, 2,895 readmissions were registered. There were relatively small differences in the frequency of readmission among the three surgical methods except for LRP performed during 2000-2002, when 22% of the men were readmitted. In that time period was the surgical method first introduced with few procedures performed. A higher risk of readmission was associated with earlier calendar period, higher age, tumor risk category, CCI and lower hospital surgical volume (table 7). However, a wide range of readmission frequency was observed among hospitals with small surgical volumes (figure 6).

**Figure 6.** Readmission rates vs surgical volume of RPs performed in 2000-2011
Table 7. Multivariable regression analysis of readmissions after RP by preoperative factors.

<table>
<thead>
<tr>
<th></th>
<th>Readmitted No. (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRP</td>
<td>1609 (9.8)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>LRP</td>
<td>145 (10.7)</td>
<td>1.27</td>
<td>1.06-1.53</td>
</tr>
<tr>
<td>RALP</td>
<td>563 (8.8)</td>
<td>1.13</td>
<td>0.99-1.29</td>
</tr>
<tr>
<td><strong>Calendar period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2002</td>
<td>336 (11.6)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>2003-2005</td>
<td>573 (9.0)</td>
<td>0.74</td>
<td>0.64-0.86</td>
</tr>
<tr>
<td>2006-2008</td>
<td>660 (9.7)</td>
<td>0.76</td>
<td>0.66-0.88</td>
</tr>
<tr>
<td>2009-2011</td>
<td>748 (9.3)</td>
<td>0.71</td>
<td>0.61-0.83</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>563 (8.8)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>60-64</td>
<td>718 (9.4)</td>
<td>1.04</td>
<td>0.92-1.17</td>
</tr>
<tr>
<td>65-69</td>
<td>734 (10.0)</td>
<td>1.10</td>
<td>0.98-1.24</td>
</tr>
<tr>
<td>≥70</td>
<td>302 (11.1)</td>
<td>1.17</td>
<td>1.00-1.36</td>
</tr>
<tr>
<td><strong>Risk category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>881 (8.0)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Intermediate</td>
<td>955 (10.1)</td>
<td>1.29</td>
<td>1.17-1.42</td>
</tr>
<tr>
<td>High</td>
<td>391 (13.7)</td>
<td>1.78</td>
<td>1.57-2.03</td>
</tr>
<tr>
<td><strong>CCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1844 (9.3)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>1</td>
<td>291 (10.4)</td>
<td>1.12</td>
<td>0.98-1.28</td>
</tr>
<tr>
<td>2</td>
<td>132 (12.1)</td>
<td>1.31</td>
<td>1.08-1.60</td>
</tr>
<tr>
<td>≥3</td>
<td>50 (15.7)</td>
<td>1.77</td>
<td>1.29-2.44</td>
</tr>
<tr>
<td><strong>No RPs in unit /year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>404 (11.3)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>30-149</td>
<td>1250 (9.8)</td>
<td>0.80</td>
<td>0.71-0.91</td>
</tr>
<tr>
<td>≥150</td>
<td>663 (8.6)</td>
<td>0.70</td>
<td>0.60-0.81</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>581 (10.7)</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Medium</td>
<td>810 (10.4)</td>
<td>1.01</td>
<td>0.90-1.14</td>
</tr>
<tr>
<td>High</td>
<td>585 (10.5)</td>
<td>1.03</td>
<td>0.91-1.17</td>
</tr>
</tbody>
</table>

*Excludes men with distant or regional metastases or missing data (n = 746)*

Of the 2,530 readmissions that could be further analysed 1,726 (68%) were related to adverse effects to surgery. The most common causes of readmission related to surgery were postoperative infection (3%) and bleeding (1%). In total, 2,317 men were readmitted and underwent 1,192 interventions, of which 815 (68%) were related to adverse effects to surgery. The most common interventions were cystoscopy, bladder catheterization and transurethral bladder neck incision.
In total, 12,534 men underwent RT and 24,886 RP during the study period. The controls were 186,624. Men treated with RT were generally older and had higher CCI compared to men that were treated with RP. Locally advanced cancer was more common among men who received RT but low-risk cancer was more common among men that received RP.

Compared to controls was the risk of the analysed diagnoses and procedures modestly but significantly elevated after both RT and RP up to 12 years after treatment (figures 7 and 8). Specifically, urinary incontinence was strongly elevated after RP and remained elevated at 12 years after surgery. In total, 1,274 (5%) men were diagnosed with urinary incontinence after RP and 167 (1%) after RT. In the RP cohort was the risk of LUTS elevated up to three years after surgery but was similar to the risk in the background population thereafter whereas the risk of LUTS remained elevated in the RT cohort in all time intervals after treatment.

In a multivariable analyses the risk for adverse effects was compared between RT and RP. During the full study period was the risk of diagnoses and procedures indicating adverse effect higher after RT. The first three years after treatment was the risk of diagnoses similar after RT and RP, but with longer follow-up, risk became higher after RT. As suspected was the risk of storage LUTS and gastrointestinal adverse effects higher after RT and risk of urinary incontinence was much higher after RP. Risk of obstructive LUTS was higher after RP up to three years after treatment but the opposite was true 3-12 years after treatment. Similarly, was the risk of procedure on the lower urinary tract or gastrointestinal procedure higher after RT but risk of a procedure for urinary incontinence was higher after RP. The most common procedure on the gastrointestinal tract after RT was endoscopy, such as proctoscopy, sigmoidoscopy and colonoscopy.
Figure 7. IRRs of receiving the analysed diagnoses after RT and RP compared to controls.
Figure 8. IRRs of receiving the analysed procedures after RT and RP compared to controls.
**Paper IV**

In totalt 8,500 men underwent RARP and 11,212 underwent RRP during the study period. Approximately 95% and 93% of men that underwent RRP and RARP respectively, were younger than 70 years. Men in the RARP cohort had a higher educational level but more men in the RRP cohort had low-risk prostate cancer. In the early part of the study period was the robot-assisted technique new and only performed at few hospitals in Sweden. Most radical prostatectomies were performed with the more conventional retropubic approach. Thus, longer follow-up was available for RRP. This likely also explains why more men in the RRP cohort had a low-risk cancer. In the early study period was a low-risk cancer indication for curative treatment but in the later period did the National Guiedelines recommend active surveillance as first line treatment for low-risk cancer.

The main results are presented in table 8. Risk of urinary incontinence was comparable between the surgical techniques but risk of obstructive LUTS was lower after RARP as compared to RRP and that difference was more prominent between 2009 and 2014 when the RARP had become an established surgical method in Sweden. However, the difference in risk of obstructive LUTS decreased with longer follow-up and was only statistically significant up to three years after surgery. Similarly, the risk of undergoing procedures for obstructive LUTS or urethrocystoscopy was lower after RARP but only up to three years after surgery.

**Table 8.** Number of events and relative risk of adverse effects of RARP vs RRP

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Full study period</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRP n = 11169</td>
<td>RARP n = 8465</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1794</td>
<td>1112</td>
</tr>
<tr>
<td>Obstructive LUTS</td>
<td>2157</td>
<td>555</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>2313</td>
<td>1162</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>191</td>
<td>232</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>385</td>
<td>171</td>
</tr>
<tr>
<td>Obstructive LUTS</td>
<td>1951</td>
<td>469</td>
</tr>
<tr>
<td>Repair of inguinal hernia</td>
<td>1335</td>
<td>643</td>
</tr>
<tr>
<td>Repair of incisional hernia</td>
<td>107</td>
<td>123</td>
</tr>
<tr>
<td>Urethrocystoscopy</td>
<td>4131</td>
<td>1781</td>
</tr>
</tbody>
</table>
No difference was observed between RARP and RRP regarding risk of diagnoses or procedures for inguinal hernia but risk of incisional hernia was higher after RARP, both when analysing diagnostic and surgical codes.

Approximately 58% of all RARPs were performed at high-volume hospitals but only 10% of RRPs. In contrast, 63% of RRPs were performed at low-volume hospitals but only 18% of RARPs. Hospital surgical volume was an important confounder that was adjusted for. For example, when not adjusting for hospital surgical volume was relative risk RARP vs RRP 1.80 (95% CI 1.32-2.46) compared to RR 1.48 (95% CI 1.01-2.16) after adjusting for that confounder.
Discussion

Information on PSA testing

In paper I, the results showed that only about 14% of men in the survey recalled having received written or both oral and written information on the pros and cons of PSA testing prior to blood draw. In 2007, National Guidelines on detection, diagnostic work-up and treatment of prostate cancer were issued by the National Board of Health and Welfare in Sweden [147]. These guidelines recommended that all asymptomatic men considering PSA testing should receive written information on the pros and cons of the PSA test prior to blood draw. To that end, a brochure with patient information was published to be used as decision aid [148]. There was only a small, clinically insignificant, increase in the proportion of men who had received written information after the National Guidelines had been issued. Furthermore, no difference was observed in the proportion of men who had been informed in any way. Approximately 22% of the men reported that they had received information about PSA testing from the media, a higher proportion than men that had received written information from their healthcare provider. This may indicate that a brochure is perhaps not the most effective decision aid. Modern decision aids, using for example social media, might reach more men and have greater impact on the proportion of men that make informed decision about screening for prostate cancer with a PSA test.

The main strength of the study is the high response rate which was approximately 90% to the mailed questionnaire and the high capture rate of the NPCR that was use to select study subjects. The study also has some limitations. First, only men with prostate cancer were included limiting the applicability of the results. Second, the results are susceptible to recall bias. When the study subjects were selected it could take up to two years until the registration in the NPCR was completed. Thus, the questionnaire was sent out 2-3 years after the diagnosis of prostate cancer. This might at least partly explain why 10% of the men were not aware that they had undergone PSA testing.

Previous studies have shown that men in general have little knowledge about prostate cancer [149] and healthcare providers often focus on the pros of PSA testing [150]. This highlights the importance of providing men with balanced, evidence-based information on the pros and cons of PSA testing. However, not all men use the decision aids provided. Partin et al. found that only about half of men used the decision aid [151].
Our results are in line with previous study from the United States where physicians were asked about prostate cancer screening practices and only 10% reported that they used written information to support the patient’s decision [152]. There is consensus that men need to be well informed before a PSA test but the current study indicates that improvements in the distribution of information and the use of decision aids are warranted.

**Readmission after radical prostatectomy**

In paper II, hospital readmission rate was used as a broad indicator of quality of care. This has been done previously in medicine. In 2012 the Centers for Medicare and Medicaid Services started a program to reduce the hospital readmissions, primarily with financial penalties levied against hospitals with readmission rates that were deemed to be excessive [153].

The overall frequency of readmissions within 90 days after surgery was approximately 10% and there were relatively small differences in readmission frequency between the three surgical methods although the frequency was higher after LRP in the time period 2000-2002. The high initial readmission rate after LRP is likely due to the learning curve. In contrast were the readmission rates comparable between RARP and RRP two years after the robot-assisted method was introduced suggesting a shorter learning curve for RARP.

The hospitals with highest surgical volume had similar readmission rates that were around 10% but low volume hospitals did have the highest and lowest readmission rates. This is likely a result of larger effect of random variation in hospitals with smaller numbers of events. Nevertheless, some low volume hospitals might have better perioperative care than high volume centers and it might be prudent to assess the perioperative care at hospitals with high readmission rates.

No association was found between educational level and readmission rates. This is in contrast to what Arbaje *et al.* observed in a cohort study from the United States using data from Medicare claims where socioeconomic factors were associated with higher risk of early readmission [154]. The equal access, tax financed health care and narrow distribution of socioeconomic status in Sweden likely explains the difference.

Shorter hospital stay was not associated with higher readmission rate indicating that protocols aiming to shorten the perioperative stay are not likely to lead to an increased readmission rate. However, the risk of
readmission was not independent of the duration of perioperative stay because short-term postoperative adverse effects lead to longer hospital stay as well as higher readmission rates.

Strengths of the study include the population based, nationwide cohort including data on virtually all radical prostatectomies performed in Sweden during the study period. The study also has some limitations. The use of administrative data was the main limitation but discharge codes of diagnoses, used in the study, have been found to be 88% to 90% accurate [155]. Another limitation was a low coverage in the National Patient Register of radical prostatectomies performed by private healthcare providers. Data on radical prostatectomies performed at private hospitals before 2007 is not available in the NPCR. Between 2007 and 2011 approximately 1,040 of 9,843 (11%) radical prostatectomies were performed at private hospitals and registered in the NPCR. However, only 296 (28%) of those operations were also documented in the National Patient Register. Thus, approximately 72% of the operations could not be further analysed as the date of surgery could not be retrieved. In this subgroup of men, including 1,040 cases, treated at private hospitals and registered in the National Patient Register, 39 (4%) were readmitted within 90 days from surgery. This suggest that the readmission rates were lower at private hospitals but low coverage of the subgroup in the National Patient Register limits the conclusions that can be drawn. Because the former subgroup was quite small, the results in the main analysis of the study should be representative of the Swedish population.

The readmission rates are similar to those in other countries. In a study from Taiwan 9% of patients were readmitted within 90 days [156]. Two single center studies from the United States showed that the readmission rates were approximately 5% [157, 158]. In a register study from England, based on data for all 18,027 radical prostatectomies in English National Health Service hospitals between 1997 and 2004, approximately 20% were readmitted within a year [159].

**Adverse effects after curative treatment**

In papers III and IV was the risk of adverse effects after curative radiotherapy and radical prostatectomy assessed. By comparing the treated men with prostate cancer-free men in the background population risk of adverse effects was found to be increased up to 12 years after treatment and this was true both for radiotherapy and radical prostatectomy. The pattern of adverse effects was different after radiotherapy and radical prostatectomy but quite similar after RARP and RRP. As suspected was the risk of urinary incontinence substantially higher after radical prostatectomy compared to
radiotherapy but risk of gastrointestinal diagnoses and lower urinary tract symptoms was higher after radiotherapy. Risk of all analysed diagnoses and procedures combined after treatment was higher after radiotherapy and similarly was the risk of late adverse effects higher after radiotherapy.

As in paper II were the main strengths of studies III and IV the nationwide, population-based cohort with a long and almost complete follow-up. Virtually all radical prostatectomies and curative radiotherapies during the study periods were included and the codes of diagnoses and procedures have been found to be 85-95% accurate [133, 139]. The studies also have some limitations. First, the capture of the out-patient care is lower than of the in-patient care or approximately 80% probably leading to underestimation of adverse effects treated in the out-patient care [139]. Second, mild adverse effects that did not require hospital admission or out-patient care are likely underreported. For example, only 5% of men included in paper IV received a diagnosis of erectile dysfunction after radical prostatectomy, a much lower number than observed in another study from essentially the same population that showed that a prescription for a phosphodiesterase type 5 inhibitor was filled for 33% of men after radiotherapy and 74% after radical prostatectomy [160]. Similarly, mild urinary incontinence is probably underestimated or only 6% after radical prostatectomy in paper IV compared to 21% of men in a recent report from a similar cohort [85] and questionnaire data from the NPCR showed that 14% of men reported moderate and 10% severe urinary incontinence after radical prostatectomy [128]. Furthermore, there was a discrepancy in the frequency of urinary incontinence after radical prostatectomy in paper III (5%) and IV (6%) despite the fact that the analysed codes were identical. The study period was different in the studies, 1997-2012 in paper III and 2004-2014 in paper IV. Over time, the number of registered urinary incontinence after radical prostatectomy increased from 16 events in 1997 to 1,301 events in 2014. Thus, the different study periods in paper III and IV likely explain the higher frequency of urinary incontinence observed in paper IV. Improved registration of urinary incontinence in the National Patient Register is a probable cause of the observed increase in urinary incontinence over time. However, there is no reason to believe that there is difference in registration of urinary incontinence after radiotherapy, RRP and RARP and the main results of the analyses, that is the relative risk of urinary incontinence between the treatments, are therefore not affected.

Urinary incontinence and erectile dysfunction are well documented adverse effects after radiotherapy and radical prostatectomy and there is little to add in that field of research. For example, a recent study based on the Prostate Cancer Outcome Study (PCOS) reported that at two and five years after treatment were men that underwent radical prostatectomy more likely to
have urinary incontinence or erectile dysfunction as compared to those men that did receive radiotherapy but no difference was observed in the odds of urinary incontinence and erectile dysfunction at 15 years after treatment [127].

Risk of obstructive LUTS was increased during the first three years after radical prostatectomy and decreased thereafter and the risk was lower after RARP up to three years after surgery. Similarly, risk of procedures for obstructive LUTS and urethrocystoscopy, was lower after RARP up to three years after surgery. This is in accordance with previous studies that have shown that most urethral strictures occur within the first year after surgery [100, 161] and are more common after RRP [102]. In contrast to radical prostatectomy, obstructive LUTS occurred later and the risk remained elevated up to 12 years after radiotherapy.

Risk of storage LUTS was elevated up to 12 years after radiotherapy but only the first three years after radical prostatectomy. Accordingly, in a recent study from SEER-Medicare, radiotherapy was associated with increased risk of urinary adverse effects at 10 years after treatment and thereafter [162]. In a cross-sectional survey, assessing health related quality of life (HRQOL) after radical prostatectomy and radiotherapy, no change in HRQOL was observed over time after radical prostatectomy but after radiotherapy urinary incontinence and sexual HRQOL worsened [163]. Another study from the CaPSURE Registry showed that most men experienced initial declines in HRQOL in the first two years after treatment but reached a plateau and remained stable 3-10 years after treatment. Surgery had the largest impact on sexual function and bother and on urinary function but radiotherapy had the strongest effect on bowel function [164].

Risk of gastrointestinal adverse effects was higher after radiotherapy compared to surgery up to six years after treatment but was comparable between the treatments thereafter. In a population-based retrospective cohort study from Canada Nam et al. showed that at five years after treatment, patients that received radiotherapy had higher incidence of rectal or anal procedures than did those who underwent surgery [165]. Similarly, Wallis et al. showed that risk of anorectal procedures and open surgical procedures was higher after radiotherapy but also showed that risk of urological procedures was higher after surgery [166]. The current results are in line with those results with endoscopy being the most common procedure after radiotherapy.

No statistically significant difference in the risk of inguinal hernia was observed between RARP and RRP. This is in contrast to what Stranne et al.
reported in a recent study where the risk of inguinal hernia was lower after RARP [98]. However, the current results are similar to the results from a study based on the SEER Medical dataset where Carlsson et al. showed that minimally invasive radical prostatectomy was associated with more than threefold increased risk of incisional hernia as compared to RRP [99].

**Conclusion**

Paper I showed that men were generally not informed about the pros and cons of a PSA test according to the National Guidelines with written information. Improved routines are needed to assure that men considering screening for prostate cancer make an informed decision.

Readmission within 90 days after radical prostatectomy was approximately 10% and comparable between the different surgical approaches but with wide variation among hospitals. Risks factors for readmission were age, tumor risk category and comorbidity.

Risk of adverse effects after radiotherapy and radical prostatectomy was increased up to 12 years after treatment. The pattern of adverse effects is different between radiotherapy and radical prostatectomy but quite similar between robot-assisted and retropubic radical prostatectomy. Risk of urinary incontinence is higher after surgery but risk of all adverse effects combined is higher after radiotherapy, specifically the risk of LUTS and gastrointestinal adverse effects. After RARP is the risk of obstructive LUTS lower but higher of incisional hernia as compared to RRP.
Future perspectives

There is a thin line between overdiagnosis and ‘correct’ diagnosis of prostate cancer. Although some men may benefit from early diagnosis of intermediate- or high-grade cancer others can be harmed with overdiagnosis of clinically insignificant cancer. The challenge is to identify men that benefit from treatment but at the same time avoid or delay diagnosis of low-grade cancer. As there is currently a number of safe and effective treatment alternatives for prostate cancer, customising the treatment plan for each individual man is essential. Given the large number of men diagnosed with prostate cancer annually, small improvements in this area can impact the life of thousands of men.

The PSA test is the most common test used currently for prostate cancer screening. However, the PSA test does have drawbacks that decreases its effectiveness. As a test used in screening it needs to have high sensitivity. Using PSA cut-off with acceptable sensitivity is associated with low specificity of the test, leading to overdiagnosis and subsequently overtreatment. Newer screening tests or methods using combination of different screening tests are promising. Furthermore, methods for implementing MRI of the prostate in the diagnosis of clinically significant cancer are evolving.

Treatments for prostate cancer have evolved dramatically during the last decades with the introduction of minimally invasive radical prostatectomy and technical improvements of radiotherapy. In spite of that, adverse effects are still common after curative treatment causing many men to experience decreased quality of life. Of those men, a substantial proportion were diagnosed with low-risk and probably clinically insignificant cancer. The use of active surveillance as a first line treatment for low-risk cancer might lower the risk of adverse effects or at least postpone them without increasing the prostate cancer-specific mortality. Newer, minimally invasive treatments with lower risk of adverse effects, such as HIFU and cryotherapy, are still under development and may be suitable for carefully selected cases.

New cytostatic and hormone therapies have improved the survival among men with metastatic prostate cancer. Further improvements in this area are expected. In the future, non-curative prostate cancer might be considered as a chronic but usually not fatal disease.

Hopefully, future diagnostic methods, improved minimally invasive surgical procedures as well as further development of medical treatment for prostate
cancer will cause the prostate cancer-specific mortality to decrease and improve the quality of life for men suffering from prostate cancer.
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