



UPPSALA
UNIVERSITET

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 1836*

Trends in Prostate Cancer Mortality

ANDRI WILBERG ORRASON



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2022

ISSN 1651-6206
ISBN 978-91-513-1484-6
URN urn:nbn:se:uu:diva-471670

Dissertation presented at Uppsala University to be publicly examined in Holmdahlsalen, Akademiska sjukhuset, ing. 100, Uppsala, Friday, 27 May 2022 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Alberto Briganti (Universita Via-Salute San Raffaele, Italien).

Abstract

Orrason, A. W. 2022. Trends in Prostate Cancer Mortality. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1836. 75 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1484-6.

In the early 20th century, cancer of the prostate was considered a rare and deadly disease with little to no possibility of cure. Since then, prostate cancer management has improved substantially with earlier detection, hormonal therapy, surgery and radiotherapy of the prostate. Nevertheless, prostate cancer remains the leading cause of cancer death in men in Western countries. The purpose of this thesis was to study trends in prostate cancer mortality including investigations of adjudication and measures of prostate cancer death.

In paper I, we studied whether increased use of radical treatment in men with locally advanced prostate cancer diagnosed between 2000-2016 has affected prostate cancer mortality in the Swedish population. The use of radical treatment almost tripled and 5-year cumulative incidence of prostate cancer death declined from 17% to 10% for all men below age 80 with locally advanced prostate cancer.

In paper II, we compared relative and cause-specific survival in all men with prostate cancer, according to age at death and risk category at diagnosis. Older men with low-risk prostate cancer at diagnosis had a substantially higher relative survival compared to cause-specific survival, 116% vs. 96% at five years after diagnosis. Despite efforts to increase comparability of expected survival, relative survival remained above 100% in these men due to healthy selection bias.

In paper III, we assessed the amount of evidence in support of prostate cancer as the cause of death by review of health care records for 495 men who between 2011-2018 died of prostate cancer according to the Cause of Death Register. Older men and men with low-risk prostate cancer at diagnosis had considerably less evidence in support of prostate cancer death compared with younger men and men with high-risk disease.

In paper IV, we applied a simulation model to estimate the lifetime risk of prostate cancer for different levels of diagnostic activity and life expectancy. Men exposed to high diagnostic activity had five-fold life-time risk of low or intermediate-risk prostate cancer and half the lifetime risk of high-risk or metastatic prostate cancer compared to men exposed to low diagnostic activity. Long life expectancy moderately increased the lifetime risk of prostate cancer in all risk categories, especially high-risk disease.

Keywords: prostate cancer, mortality, survival, death certificate, adjudication, lifetime risk, diagnosis, life expectancy

Andri Wilberg Orrason, Department of Surgical Sciences, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

© Andri Wilberg Orrason 2022

ISSN 1651-6206

ISBN 978-91-513-1484-6

URN urn:nbn:se:uu:diva-471670 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-471670>)

To Leifur Guðmundsson – my grandfather

Cover photo from the book *De Humani Corporis Fabrica Libri Septem* (printed in 1543) by the founder of modern anatomy, Andreas Vesalius (1514–1564) from Brussels. Vesalius was the first anatomist to illustrate the prostate and to describe it as a single organ.

List of Papers

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

- I Orrason, A.W., Westerberg, M., Garmo, H., Lissbrant, I.F., Robinson, D., Stattin, P. (2020) Changes in treatment and mortality in men with locally advanced prostate cancer between 2000 and 2016: a nationwide population-based study in Sweden. *British Journal of Urology International*, 126(1):142-151.
- II Orrason, A.W., Garmo, H., Styrke, J., Dickman, P.W., Stattin, P. (2021) Comparison of relative survival and cause-specific survival in men with prostate cancer according to age and risk category: a nationwide, population-based study. *American Journal of Epidemiology*, 190(10):2053-2063.
- III Orrason, A.W., Styrke, J., Garmo, H., Stattin, P. (2022) Evidence of cancer progression in men with prostate cancer as the adjudicated cause of death. Manuscript under review.
- IV Orrason, A.W., Westerberg, M., Albertsen, P., Styrke, J., Robinson, D., Garmo, H., Stattin, P. (2022) Diagnostic activity impacts lifetime risk of a prostate cancer diagnosis more strongly than life expectancy. Manuscript submitted.

Reprints were made with permission from the respective publishers.

Contents

Introduction.....	13
Background.....	14
Epidemiology.....	14
Risk factors.....	15
Diagnosis.....	16
Prostate cancer screening by use of PSA testing.....	17
Staging.....	17
TNM staging system.....	17
Gleason grading.....	18
Risk categories.....	18
Locally advanced prostate cancer.....	19
Measures of prostate cancer survival and mortality.....	20
Analysis of survival.....	20
Net survival.....	20
Relative survival.....	20
Cause-specific survival.....	21
Crude probability of death.....	21
Mortality.....	22
Adjudication of prostate cancer death.....	23
Lifetime risk.....	24
Aims of the studies.....	26
Materials and Methods.....	27
Data registers.....	27
The National Prostate Cancer Register.....	27
Prostate Cancer data Base Sweden (PCBaSe).....	27
Paper I.....	28
Study design.....	28
Statistical analysis.....	29
Paper II.....	29
Study design.....	29
Statistical analysis.....	29
Paper III.....	30
Study design.....	30
Statistical analysis.....	33

Paper IV	34
PRISM-PC simulation model	34
Study design	35
Ethical considerations	36
Data collection and registration	36
NPCR	36
PCBaSe	36
Risk assessment	37
Ethical approvals	37
Results	38
Paper I	38
Paper II	44
Paper III	47
Paper IV	49
Discussion	51
Paper I	51
Paper II	53
Paper III	54
Paper IV	56
Conclusions	58
Future perspectives	59
Swedish summary	62
Bakgrund	62
Delarbete I	62
Delarbete II	63
Delarbete III	63
Delarbete IV	64
Slutsatser	64
Acknowledgements	65
References	66

Abbreviations

ADT	Androgen Deprivation Therapy
APC	Age-Period-Cohort
ART	Androgen Receptor Targeted drugs
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DCE	Direct Contrast Enhancement
DCI	Drug Comorbidity Index
DRE	Digital Rectal Examination
DWI	Diffusion Weighted Imaging
EAU	European Association of Urology
GGG	Gleason Grade Group
GnRH	Gonadotropin Releasing Hormone
HR	Hazard Ratio
ICD-10	International statistical Classification of Diseases and related health problems–10th revision
INCA	Information Network for Cancer care
ISUP	International Society of Urological Pathology
LUTS	Lower Urinary Tract Symptoms
NCCN	National Comprehensive Cancer Network
mpMRI	Multiparametric Magnetic Resonance Imaging
NPCR	National Prostate Cancer Register
PET/CT	Positron Emission/Computed Tomography
PI-RADS	Prostate Imaging Reporting and Data System
PRISM-PC	Proxy- based Risk- stratified Incidence Simulation Model – Prostate Cancer
PSMA	Prostate-Specific Membrane Antigen
PSA	Prostate Specific Antigen
RCC	Regional Cancer Center
ROI	Region of Interest
SCB	Statistiska centralbyrån
SEER	Surveillance, Epidemiology, and End Result
SKR	Swedish Association of Local Authorities and Regions
SoS	Socialstyrelsen
SPCG-7	Scandinavian Prostate Cancer Group 7
TRUS	TransRectal UltraSound

Overview of papers

Paper	Design	Main exposures	Endpoints	Main findings
I	Population-based retrospective cohort study	Calendar year of diagnosis as proxy for radical treatment	Cumulative incidence of prostate cancer mortality	Increased use of radical treatment led to decreased prostate cancer mortality
II	Population-based retrospective cohort study	Age and risk category	Relative and cause specific survival	Relative survival was higher than cause-specific survival in older men with low-risk prostate cancer
III	Retrospective cohort study	Age and risk category	Evidence of prostate cancer as cause of death	Old age and low-risk prostate cancer at diagnosis was associated with less evidence of prostate cancer as cause of death
V	Simulation study	Diagnostic activity and life expectancy	Lifetime risk of a prostate cancer diagnosis	High diagnostic activity and long life expectancy increased lifetime risk of prostate cancer

Introduction

Prostate cancer is the most common malignancy in men in Europe and accounts for around a fourth of all cancer diagnosis in men¹. Management of prostate cancer has evolved substantially in the last decades with earlier detection and improved treatment such as radical prostatectomy, radiotherapy of the prostate and hormonal therapy. Death due to prostate cancer is still high and accounts for around 10% of all cancer-related deaths in men in Europe¹. Most men who die of prostate cancer have multiple bone metastases before death, causing significant morbidity and pain².

An understanding of mortality statistics is essential to evaluate the burden of prostate cancer as well as the effects of early detection and treatment. In this thesis I first investigated how changes in treatment of men with locally advanced prostate cancer has affected mortality in Sweden. Next, different methods to estimate prostate cancer survival were compared in detail. Then, the underlying evidence behind the adjudication of prostate cancer death was investigated. In the last paper the lifetime risk of a prostate cancer diagnosis was evaluated in relation to diagnostic activity and life expectancy.

Background

Epidemiology

Prostate cancer is the second most common cancer in men worldwide, with 414 259 new cases registered in 2020³. The age-standardized incidence of prostate cancer varies largely between geographic regions, with the highest rates in Northwestern Europe, Northern America and the Caribbean, and the lowest rates in Southeastern and South-Central Asia. The differences in incidence between countries is largely explained by variations in diagnostic activity and age composition of the population since around half of all men have microscopically detectable prostate cancer at age 80 or older according to autopsy records⁴.

In Sweden the number of new cases has almost doubled since the early 1990's with 9 009 new cases in 2020, accounting for around 25% of all new cancer diagnosis in men⁵. This rise in incidence is primarily due to the introduction of prostate specific antigen (PSA) testing that caused an increase in the total number of cases and a strong increase in the proportion of low and intermediate-risk tumours (figure 1)⁶. Increased diagnostic and therapeutic activity, and longer life expectancy have resulted in a threefold increase of prostate cancer prevalence in the last two decades with more than 100 000 men living with prostate cancer in Sweden in 2016⁷.

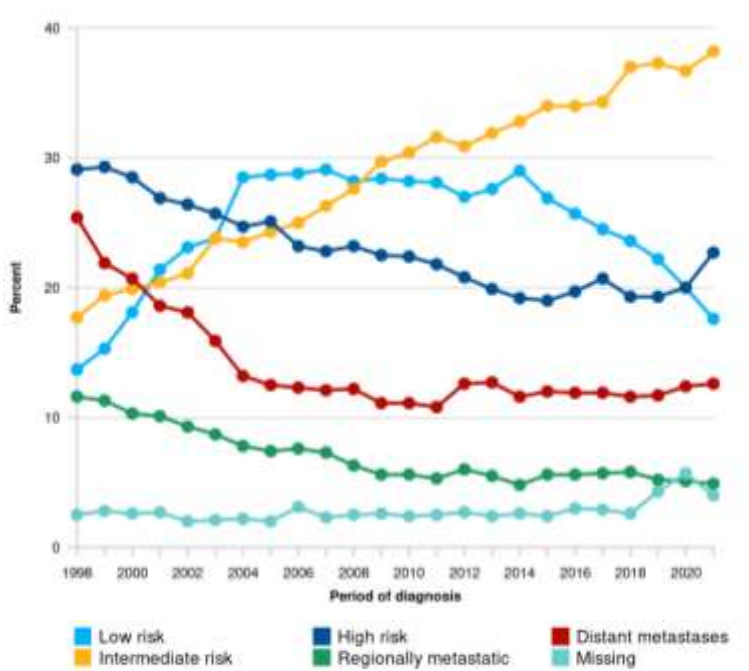


Figure 1. Distribution of risk classification for men with prostate cancer in Sweden 1998-2020. Source: National Prostate Cancer Register, <https://www.npcr.se>.

Risk factors

Currently, there are three risk factors for prostate cancer that are well established: age, ethnicity, and family history. The incidence of prostate cancer is strongly related to age; around half of all men with prostate cancer are diagnosed after age 70, whereas few men are diagnosed before age 50⁵.

Men of African and Caribbean descent have the highest prostate cancer incidence worldwide, whereas Asian men have the lowest risk⁸. Data from the Surveillance, Epidemiology and End Result (SEER) database in the United States shows that African-American men are more than two times more likely to die from prostate cancer than white men of the same age⁹. It is still debated whether this difference is due to differences in socioeconomic status and access to health care or if certain ethnic groups are inherently predisposed to prostate cancer.

According to twin studies, prostate cancer has one of the highest heritability of any other cancer, accounting for up to 57% of the variability in prostate cancer risk¹⁰. Men who have a first degree relative with a history of prostate cancer are 2-3 times more likely to be diagnosed with prostate cancer¹¹. The risk related to family history is likely somewhat inflated by screening of fam-

ily members with increased detection of indolent tumours. However, according to a large population-based study in Sweden, men with one affected first-degree relative were more likely to be diagnosed with high-risk prostate cancer compared with men without family history of prostate cancer¹².

In another study from the SEER database, Korean-American immigrants had a higher incidence of prostate cancer compared to native South Koreans, which suggests that environmental factor could play a role in prostate carcinogenesis¹³. In a recent systematic review of dietary factors, consumption of red meat, animal fat and dairy products was associated with increased risk of prostate cancer, whereas tomatoes, soy-containing products, green tea and cruciferous vegetables may have a protective effect¹⁴. Although Western diet is associated with higher risk of prostate cancer, more prospective studies are still needed to support recommendations for dietary modifications.

Diagnosis

Despite that most prostate cancers have an indolent course, prostate cancer is still the leading cause of cancer-related death in men in Sweden⁵. The main challenge of early diagnosis is distinguishing between indolent cancers that do not require radical treatment, from cancers destined to progress if not treated in time. The most widely used biomarker for the detection of prostate cancer is PSA, a glycoprotein enzyme that is produced by both benign and malignant cells of the prostate. The main function of PSA is to liquify semen by breakdown of the seminal coagulum, that enables spermatozoa motility¹⁵. A small proportion of PSA naturally leaks from benign prostate cells into the bloodstream. Malignant or inflamed prostate cells are more permeable and tend to leak more PSA into the circulation. Although PSA has acceptable performance in predicting subsequent diagnosis of prostate cancer, the test performs poorly at low serum PSA concentrations (<10 ng/ml), in particular due to low specificity. In a longitudinal study from Prostate Cancer Database Sweden (PCBaSe) no PSA cut-off attained positive and negative likelihood ratios that are formally regarded as sufficiently high for decision-making¹⁶. Furthermore, PSA alone is a poor marker to distinguish between indolent and high-risk tumours. Several efforts have been made to increase the sensitivity and specificity of the test e.g. age-specific thresholds, the proportion of free versus total PSA, and PSA density i.e. serum levels in relation to prostate volume^{17,18}.

Diagnosis of prostate cancer is confirmed by biopsy of the prostate, following a work-up of elevated PSA, suspicious finding on digital rectal examination (DRE) or imaging. Transrectal ultrasound (TRUS)-guided systematic random biopsies of predetermined regions in the prostate, introduced in 1989 by Hodge and colleagues, is still one of the most widely used methods and currently consists of 10-12 biopsy cores¹⁹. The procedure is associated with complications; up to 25% of the patients experience transient lower urinary tract

symptoms (LUTS), around 6% receive prescription for antibiotics due to infection, and 1-4% are re-admitted to hospital due to infectious complications^{20,21}.

In recent years multiparametric magnetic resonance imaging (mpMRI) of the prostate has emerged as an important diagnostic tool to distinguish between indolent and clinically significant tumours prior to biopsy. The technique consists of T2 weighted sequences with diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE). The reporting of imaging results has been standardized through the Prostate Imaging Reporting and Data System (PI-RADS) score that classifies the likelihood of a region of interest (ROI) to contain a significant cancer from a score of one to five. A PI-RADS score of five represents a very high risk of clinically significant cancer and a score of three is equivocal. The chance of detecting a clinically significant cancer in men with a PSA density $\leq 0.15 \mu\text{g}/\text{l}/\text{cm}^3$ and PI-RADS ≤ 3 is low, hence if biopsy is not performed under these circumstances, around a fourth of men with PSA 3-10 $\mu\text{g}/\text{l}$ avoid unnecessary biopsy²²⁻²⁴.

Prostate cancer screening by use of PSA testing

Two large randomized clinical trials have studied the effect of PSA screening on prostate cancer mortality^{25,26}. In the European Randomized Study of Screening for Prostate Cancer, screening lowered the risk of prostate cancer death by 21%²⁵. For each averted death due to prostate cancer 27 additional prostate cancer diagnoses were made. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found no significant difference in prostate cancer mortality between experimental arm and control arm²⁶. However, the results of the trial likely reflect heavy contamination due to opportunistic PSA testing in the control arm. Whether the benefit of early detection with organized PSA screening outweighs the harm of overdiagnosis is still debated²⁷.

Staging

TNM staging system

The extent and spread of a prostate cancer is based on the three key elements of the TNM system, published by the Union of International Cancer Control and the American Joint Committee on Cancer, latest revision in 2017²⁸.

The tumour stage, T1-T4, is based on an assessment of the tumour within the prostate. T1a and T1b represents incidentally detected prostate cancer during transurethral resection of the prostate and T1c is prostate cancer detected in a work-up of an elevated PSA with no tumour detected by DRE or imaging. T2 tumours are confined within the prostate and are either palpable by DRE or visible on imaging. T3-T4 tumours extend through the prostatic capsule

(T3a), invade the seminal vesicles (T3b) or other organs of the pelvic region (T4), in most cases the bladder neck.

Lymph node metastasis in the pelvic region is described by stage N1, and metastasis to lymph nodes outside the pelvis is described by stage M1a. Metastasis to bone and visceral organs is represented by M1b and M1c.

Gleason grading

Gleason grading is the most common system to histologically grade prostate cancer and describes the architectural pattern of the prostate cancer tissue, ranging from well differentiated, Gleason grade 1, to very poorly differentiated, Gleason grade 5^{29,30}. Adenocarcinomas of the prostate usually have a histologically heterogenous appearance. The grading is therefore presented as the sum of the two most dominant patterns by a score-based system, the Gleason score, ranging from 2-10. In 2005 the International Society of Urological Pathology (ISUP) recommended that the highest grade-pattern should be incorporated in the Gleason score instead of the second most dominant pattern³¹. Additionally, regular cribriform glands were graded as Gleason grade 4 which were previously considered grade 3. This grade migration has resulted in an inflation of the Gleason score, which makes it difficult to compare survival in men with prostate cancer based on Gleason score between time periods before and after 2005¹⁶. In 2014 the Gleason score was further classified into relevant prognostic groups, Gleason Grade Groups (GGG) 1-5, in which Gleason score 7 is separated into two groups, GGG 2: 3+4 and GGG 3: 4+3³². The tumour grade is the single most important predictor of tumour progression and relapse after treatment^{33,34}. Several other terms are currently used for the Gleason Grade Groups, and there is currently a heated debate on the use of proper terminology³⁵.

Risk categories

The stratification of prostate cancer by risk of progression is the main factor that determines the choice of cancer management. This can be obtained by merging the TNM stage, Gleason score and PSA. In the four studies of this dissertation we defined risk categories according to a modification of the National Comprehensive Cancer Network (NCCN) categorisation³⁶:

- 1) Low-risk: clinical stage T1-T2, Gleason score 6 and PSA < 10 ng/ml
- 2) Intermediate-risk: T1-T2 and Gleason score 7 or PSA 10-19.9 ng/ml
- 3) High-risk or locally advanced: T3, Gleason score \geq 8 or PSA 20-49.9 ng/ml
- 4) Regional: T4, N1 or PSA 50-99.9 ng/ml
- 5) Distant metastases: M1 or \geq 100 ng/ml

In essence we divided the NCCN metastatic category into regional and distant metastases based on different outcomes in analysis of survival for men in NPCR³⁷.

Locally advanced prostate cancer

In paper I we specifically focus on men with locally advanced prostate cancer which warrants more information on this risk group. Around 10% of all men diagnosed with prostate cancer have locally advanced disease at presentation i.e. invasion of the prostate capsule with or without invasion of the seminal vesicles or other pelvic organs⁶. Locally advanced tumours often have high GGGs and according to a series of 5 274 men treated with radical prostatectomy and pelvic lymph node dissection, 16-26% had metastasis to pelvic lymph nodes³⁸. Men with locally advanced tumours are therefore at high risk of tumour progression and have a poor prognosis without curative treatment³⁹. According to a population-based study of 12 184 men with locally advanced prostate cancer managed with noncurative intent, 8-year prostate cancer specific mortality was 28% for GGG 1 and 64% for GGG 5⁴⁰.

The management of locally advanced prostate cancer has evolved in the past decades. The first randomized trial to study the effects of radiotherapy vs. hormone therapy by orchidectomy failed to show survival difference between treatment groups due to lack of statistical power⁴¹. Later, the addition of long-term (≥ 2 years) adjuvant androgen deprivation therapy (ADT) to radiotherapy was shown to benefit overall survival^{42,43}. At the turn of the century, two large randomized trials revealed a survival benefit of combining radiotherapy with neoadjuvant and adjuvant ADT compared to ADT only in men with locally advanced prostate cancer^{44,45}. In the Scandinavian Prostate Cancer Group 7 (SPCG-7) trial, absolute risk of prostate cancer mortality at 10-years follow-up was reduced by nine percent⁴⁵. This difference continued to increase to 17% at 15-years follow-up³⁴. Considering these results, both the European Association of Urology (EAU) and Swedish National guidelines recommend radiotherapy and ADT for men with locally advanced prostate cancer and a life expectancy of five years or more^{46,47}.

The role of radical prostatectomy for locally advanced prostate cancer is still unclear. The risk of positive surgical margins after prostatectomy is considerably higher for locally advanced compared to organ-confined disease, which is a strong predictor for prostate cancer recurrence and mortality^{48,49}. Observational studies have shown similar survival outcomes for radiotherapy and radical prostatectomy as a part of multimodal therapy for locally advanced prostate cancer, and some even favouring radical prostatectomy⁵⁰⁻⁵². Observational comparisons are difficult to interpret due to confounding by indication of treatment, as men with more advanced cancer characteristics are more likely to receive radiotherapy⁵³. Currently, the SPCG-15 trial is ongoing with the purpose of comparing these two treatment alternatives head-to-head⁵⁴.

The use of curative treatment for locally advanced prostate cancer has increased in Sweden and in other countries^{55,56}. Whether these trends have led to a decrease in prostate cancer mortality on a population level is unclear since the treatment effects of previous randomized trials may not be fully translatable to a more heterogeneous real-world population.

Measures of prostate cancer survival and mortality

Analysis of survival

Survival is the analysis of any time-to-event data e.g. time from treatment until relapse or time from diagnosis until death. Survival is frequently estimated with the non-parametric Kaplan-Meier estimator that calculates the proportion of subjects who have not experienced the event of interest during a specific time interval⁵⁷. Subjects lost to follow-up e.g. due to drop-out or emigration are censored and not included in the denominator for survival estimation. Analysis of time until death of any cause is defined as overall survival, whereas the term cause-specific survival is applied if deaths related to other causes than the event of interest are censored.

Net survival

Net survival is defined as the survival observed if death can only occur due to the disease of interest and is a measure of cancer care that reflects the effects of early detection and treatment on cancer death^{58,59}. Net survival is not affected by primary prevention or competing causes of death, whereas it can be affected by lead-time and length bias due to early detection of indolent tumours. These biases may lead to overestimation of survival without any prolongation of life. Nonetheless, lead-time and length bias can be minimized by stratification of survival by prognostic risk groups at diagnosis. Net survival can be measured by two frameworks: relative survival and cause-specific survival.

Relative survival

Relative survival, which is independent of cause of death, is defined as the ratio of the observed overall survival in the study population and the expected survival if the study population was free of the disease of interest⁶⁰. Relative survival is the preferred method in population-based cancer studies as it is not affected by misclassification of cause of death, and also accounts for any indirect effects of the cancer or its treatment on death^{61,62}. The expected survival is calculated using data from general population life tables, stratified by age,

sex and calendar year of birth. Stratification by other factors such as comorbidity and socioeconomic status is rarely available. Relative survival may therefore be subject to incomparability bias e.g. men with prostate cancer might differ in many ways from the general population in terms of health seeking behaviour and comorbidity, rendering relative comparisons of survival difficult to interpret. This is especially true for cancers highly related to specific risk factors e.g. lung cancer and smoking, since death due to cardiovascular disease and other cancers is more common in men with lung cancer compared with the general population⁶³.

Cause-specific survival

Cause-specific survival depends on correct attribution of cause of death since other causes than the disease under study are censored. This method is more suitable for calculating net survival in a clinical trial since the cause of death has usually been reviewed by an expert committee. Cause-specific survival is also useful in subgroup analysis since lifetables rarely include data on specific risk factors in the general population. However, analysis of cause-specific survival in population-based studies relies solely on official death certificates that may be subject to misclassification errors^{64,65}. Furthermore, cause-specific survival does not account for contributing effects on death from the disease of interest due to the binary nature of death certification.

Several registry-based studies have compared relative and cause-specific survival for different cancer types^{61-63,66-68}. In these studies, relative survival is lower compared to cause-specific survival for most malignancies, with the exception of screen-detected tumours e.g. prostate and breast cancer. Due to biases in both frameworks the true net survival for men with prostate cancer has been difficult to estimate⁶⁹. Previous studies comparing relative and cause-specific survival for men with prostate cancer have not included sufficient information on risk category and age at diagnosis, both which could affect these biases differently.

Crude probability of death

Net survival is a useful measure for studying temporal trends and population differences as it is unaffected by changes in competing risks i.e. the risk of death by other causes than the disease of interest. However, the hypothetical situation in which death can only occur due to a certain disease hardly reflects real-world situation.

The crude probability of death, also named cumulative incidence of mortality, accounts for competing risks of death and reflects the actual probability of dying from the disease of interest⁵⁸. This measure is of interest to clinicians and patients with prostate cancer, since the actual risk of dying from prostate cancer is affected by the risk of dying from other causes. This is particularly important for old men with prostate cancer who are at high risk of dying from competing causes. In a study by Eloranta et. al, men age 75 with intermediate or high-risk prostate cancer treated conservatively were predicted to have 27% net probability of prostate cancer death, compared to only 18% crude probability of death at 10-year follow-up (figure 2)⁷⁰. The crude probability of prostate cancer death is always lower than the net probability of prostate cancer death, and this difference tends to increase with age since dying of other causes becomes gradually more likely.

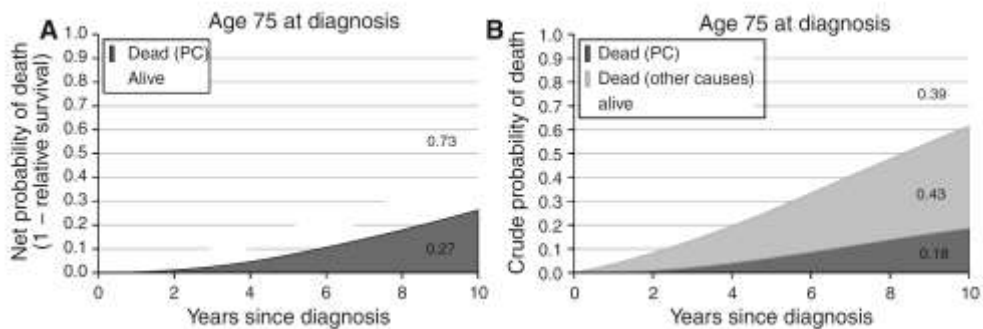


Figure 2. Predictions of net probabilities (A) and crude probabilities (B) of death due to prostate cancer for men age 75 at diagnosis with intermediate or high-risk prostate cancer treated conservatively or with hormonal treatment in the National Prostate Cancer Register of Sweden between 1996 and 2008. Source: Eloranta et. al. How can we make cancer survival statistics more useful for patients and clinicians: An illustration using localized prostate cancer in Sweden⁷⁰.

Mortality

Mortality is defined as the proportion of deaths in a population for a specified period, usually expressed as the number of deaths per 100 000 individuals in one year for a given population. Mortality is an important statistic as a measure of progress in cancer care and is not influenced by lead-time or length bias. Changes in mortality may be difficult to interpret since it is affected by multiple factors e.g. primary prevention (preventing the cancer before it occurs), secondary prevention (early detection of cancer) and implementation of new treatment strategies⁵⁹.

Although most men die with but not from prostate cancer, the disease still accounted for 375 304 deaths worldwide in 2020 or around 4% of all cancer-

related deaths⁷¹. In Sweden, prostate cancer is the most common cause of cancer-related death⁷². Prostate cancer mortality declined from 29 to 19 deaths per 100 000 men in Sweden between 1998 and 2020. This decline is likely a result of advances in prostate cancer management with more precise and earlier diagnosis as well as increased use of both radical and life-prolonging treatments including earlier use of ADT. In men below age 80, mortality declined more than 50%, or from 16 to 7 deaths per 100 000 men, whereas for men age 80 or older, the mortality decline was less pronounced, from 835 to 625 deaths per 100 000 men, i.e. a decrease of 25% (figure 3)⁷².

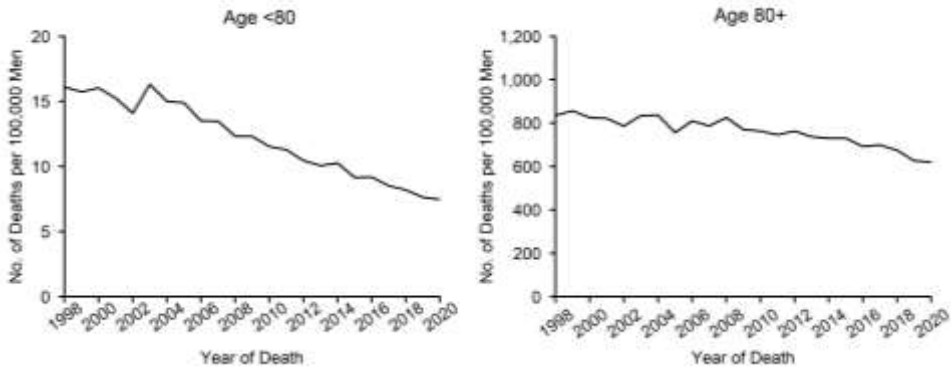


Figure 3. Prostate cancer mortality (age-standardized to the world population) in Sweden between 1998 and 2020. Source: Data from the National Board of Health and Welfare, https://sdb.socialstyrelsen.se/ef_dor/val.aspx.

There may be several reasons for a less distinct decrease in mortality in older men. First of all, older men are less likely to be diagnosed with screen-detected tumours, and a large proportion of older men present with symptomatic, advanced prostate cancer⁷³. Secondly, due to comorbidity and shorter life expectancy, older men are less likely to receive radical treatment⁷⁴. Furthermore, use of life-prolonging treatment in younger men will postpone death due to prostate cancer for some men, and as a result more men die at old age. Lastly, an increase in the prevalence of prostate cancer among older men could result in over-reporting of prostate cancer deaths due to higher risk of misclassification errors in death certification in older men^{64,65}.

Adjudication of prostate cancer death

Correct adjudication of cause of death is essential to correctly interpret mortality, cause-specific survival and crude probability of death. In Sweden, the underlying cause of any death is registered by the cause of death certificate in the Cause of Death Register⁷⁵. This certificate allows for one underlying and 48 contributing causes of death. The World Health Organisation defines the

underlying cause of death according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) as follows⁷⁶:

“(a) the disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury”

The accuracy of the physicians responsible for certifying the cause of death influences the quality of the register. In a hospital setting, death certification is often performed by junior physicians who may not always be familiar with the certification rules. Death at old age at a nursery or at home may be difficult to adjudicate due to limited documentation of follow-up. Furthermore, separating the underlying cause of death from contributory causes is challenging in patients with multiple comorbidities.

At the Cause of Death Register, identification of the underlying cause of death is coded according to ICD-10 rules with the assistance of automated classification software. Around 50% of the death certificates are coded fully by the software, whereas the rest is coded manually by professional coders at the Cause of Death Register⁷⁵.

The quality of death certificates for men with prostate cancer is high according to medical review of death in participants of randomized controlled trials⁷⁷⁻⁷⁹. However, these men are usually younger, healthier, and followed up more closely than the general population.

Population-based studies on the quality of death certificates in men with prostate cancer show conflicting results^{64,75,80,81}. In a study from Sweden, and in a more recent study from Norway, prostate cancer death was over-reported in the Cause of Death Register compared with adjudication after review of available evidence in medical notes^{64,75}.

Without autopsy, the adjudication of cause of death depends on the physician's assessment of the evidence at hand. The adjudication of death in old men and men with low-risk prostate cancer could be affected by a sticky-diagnosis bias i.e. erroneously attributing prostate cancer as cause of death due to an existing prostate cancer diagnosis⁸². Previous studies on the quality of death certification in men with prostate cancer have not presented the amount of evidence in support of prostate cancer as the cause of death in the adjudication process.

Lifetime risk

Lifetime risk is defined as the risk of experiencing a certain event at least once over the course of a lifetime and is frequently used to communicate cancer risk to the general population. The lifetime risk of a disease for a specific birth

cohort is commonly estimated from age-specific incidence and mortality rates applying the current probability method as described by Goldberg et al⁸³. Importantly, this method accounts for competing events i.e. death due to other causes than the disease of interest. Cumulative risk is another statistic that calculates the risk of disease at a given upper age limit⁸⁴. This statistic is non-dependent on competing risk e.g. the cumulative risk up to age 80 is defined as the risk of experiencing the event before age 80, given that you will live up to that age. Cumulative risk is therefore more appropriate for population comparisons, whereas the current probability method provides a more realistic estimate of lifetime risk⁸⁵.

In the Western world, the estimated lifetime risk of prostate cancer is high; around 1 in 6-8 men in Sweden, the United Kingdom and the United States^{12,86-88}. The lifetime risk of a prostate cancer diagnosis depends on three factors:

1. Diagnostic activity: use of diagnostic tests, frequency of prostate biopsy and number of cores obtained, and access to urology health care and imaging.
2. Life expectancy: the longer a man lives, the higher the risk of a prostate cancer diagnosis.
3. Exposure to risk factors.

The lifetime risk of a prostate cancer diagnosis is not a fixed entity since these factors may vary considerably in one lifespan. In Sweden, the introduction of PSA testing doubled the incidence of prostate cancer from 52 cases in 1990 to 104 cases per 100 000 men in 2010⁵. As a result of this dramatic rise in incidence along with increased life expectancy, lifetime risk of a prostate cancer diagnosis in Swedish men has changed substantially.

The lifetime risk of prostate cancer can be calculated using Age-Period-Cohort (APC) models that incorporate biological effects related to aging, time-trends related to periods, and cohort effects i.e. variations between generations^{89,90}. Several studies have applied these models to calculate lifetime risk of prostate cancer⁹¹⁻⁹³. A similar model, the Proxy- based Risk- stratified Incidence Simulation Model – Prostate Cancer (PRISM- PC) by Westerberg et al., is based on Swedish population data^{94,95}. Unlike other APC models, PRISM-PC also accounts for variations in diagnostic activity on the lifetime risk of prostate cancer, both overall and for each risk category. The PRISM-PC model will be used in paper IV for estimation of lifetime risk of a prostate cancer diagnosis assuming different levels of diagnostic activity and life expectancy.

Aims of the studies

The overarching aim of this thesis was to study trends in prostate cancer mortality according to age, risk category, and treatment with an emphasis on different measures of death due to prostate cancer and assessment of prostate cancer death certification.

Specific aims:

- I To investigate if increased use of radical treatment for men with locally advanced prostate cancer has led to a decrease in prostate cancer mortality on a population-basis.
- II To compare relative and cause-specific survival in men with prostate cancer according to age and risk category.
- III To assess the evidence in support of prostate cancer death in men who died of prostate cancer according to the Cause of Death Register.
- IV To study the lifetime risk of a prostate cancer diagnosis in relation to different levels of diagnostic activity and life expectancy.

Materials and Methods

Data registers

The National Prostate Cancer Register

Data on incident cases of prostate cancer has been registered in the National Prostate Cancer Register (NPCR) of Sweden since 1998. NPCR has a capture rate of 98% as compared with the Swedish Cancer Register, to which reporting is mandated by law⁹⁶. Completeness and validation of the data is checked at each of the six Regional Cancer Centers (RCC) before transmission to the Swedish Cancer Register and NPCR. Corrections and updates of previous years are made continuously. Detailed data on prostate cancer diagnosis, work-up and treatment is provided to NPCR by use of separate forms for diagnostic data, primary treatment, radical prostatectomy, radiotherapy, and transition from active surveillance to curative treatment. Since 2007 the forms are uploaded on an online platform, the Information Network for Cancer care (INCA). Variables registered include date and health care unit of diagnosis, TNM classification, Gleason score, serum levels of PSA at diagnosis, diagnostic work-up, and primary treatment delivered within six months after date of diagnosis^{97,98}. Data are reported back to each department at the INCA platform within 24 hours after reporting, and also reported on a public interactive online reporting system; RATTEN, www.npcr.se/RATTEN, which is updated twice yearly^{99,100}.

Prostate Cancer data Base Sweden (PCBaSe)

By use of the Swedish personal identity number, NPCR has been linked to several other health care registers and demographic databases, including the National Patient Register, the Prescribed Drug Register, the Cause of Death Register, the Multi-Generation Register, and the Longitudinal integration database for health insurance and labour market studies (LISA), to create PCBaSe, a database for register-based research (figure 4). New iterations of PCBaSe are created every third year and PCBaSe contains five control men per case matched to cases on birth year and county of residency. Since its inception in 2010, PCBaSe has been the basis for close to 200 peer-reviewed articles⁶.

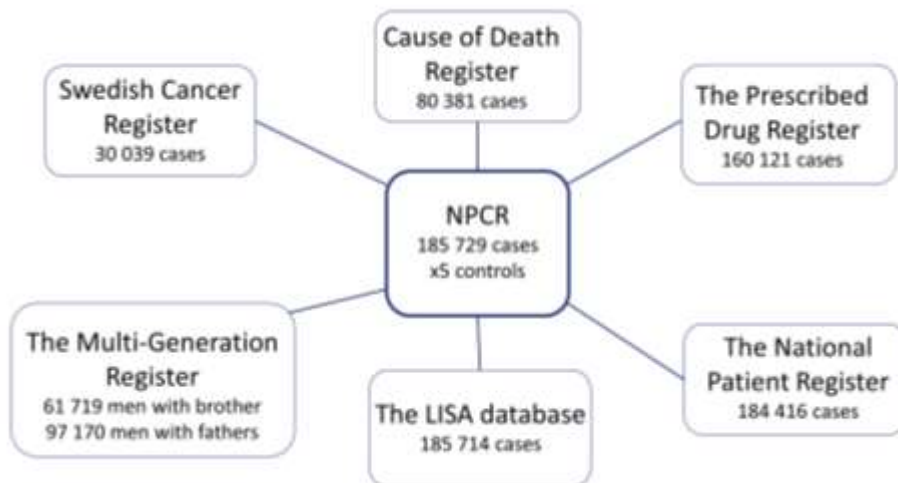


Figure 4. Prostate Cancer data Base Sweden (PCBaSe) 4.0 was created by linkages between NPCR and other health care registers and demographic databases.

Paper I

Study design

Our first paper included all men in PCBaSe diagnosed between 2000-2016 with locally advanced prostate cancer, defined as clinical local stage T3 or T4, with PSA <100 ng/ml and no evidence of metastasis (M0 or Mx), and any N stage and GGG. Primary radical treatment included radiotherapy, with or without neoadjuvant or adjuvant ADT, and radical prostatectomy. Changes in use of radical treatment and cumulative incidence of prostate cancer mortality were assessed between four calendar periods: 2000-2003, 2004-2007, 2008-2011 and 2012-2016. Results were also compared between different regions in Sweden.

Instead of directly analysing the association of radical treatment on prostate cancer mortality we focused our analysis on calendar period of diagnosis i.e. each of the four calendar periods can be considered as four arms in a “pseudo-trial“, each representing different levels of use of radical treatment. This design limits the selection bias due to treatment indication, since increased use of radical treatment in later periods is more likely a result of emerging evidence from randomized trials rather than an increase in number of patients eligible for treatment.

Statistical analysis

Cumulative incidence of prostate cancer death was assessed and plotted for the four different calendar periods according to relevant age groups. Follow-up started at date of diagnosis and ended 31 December 2017 or at date of death. Cox regression analysis was used to assess the association of calendar period with the hazard of prostate cancer death. Three analyses were performed:

- I. Unadjusted
- II. Adjusted for age, PSA, T stage, M stage, comorbidity according to Charlson Comorbidity Index (CCI)¹⁰¹, civil status and educational level
- III. Adjusted for factors in model II and primary radical treatment

In analysis II all available factors associated with both calendar period and prostate cancer death have been adjusted for, except radical treatment. Analysis II is therefore representative of the treatment effect. In analysis III we further assessed if any residual hazard remains after adjusting for radical treatment.

Paper II

Study design

Paper II included all men in PCBaSe diagnosed with prostate cancer between 1998 and 2016. Relative and cause-specific survival was compared in different age groups and risk categories. Age at diagnosis was categorized as <70, 70-79 and 80-89, excluding men 90 years or older due to short life expectancy. Risk groups were defined according to a modification of the NCCN criteria as previously described.

Statistical analysis

Relative survival was estimated with the Ederer II method and cause-specific survival was estimated with the Kaplan-Meier method^{57,60}. Expected survival was calculated using survival probabilities from Swedish population life tables, matched by age and year of the study population¹⁰². The so-called “complete” follow-up approach was applied in both methods as described by Brenner and Rachet¹⁰³.

The Pohar-Perme estimator is currently the method of choice for estimating net survival within the relative survival framework, as it adjusts for informative censoring¹⁰⁴. However, the Kaplan-Meier method does not adjust for informative censoring and since our primary aim was to compare the two frameworks of net survival, we chose to compare two commonly used estimators, neither of which adjust for informative censoring. We prioritized comparability of the estimators and recognize that both may be subject to a small bias.

To minimize incomparability bias we repeated the relative survival analysis for men age 80-89 diagnosed between 2007-2016, using a cohort of comparators in PCBaSe to calculate expected survival instead of general population life tables. The PCBaSe comparator cohort consists of five comparators for each prostate cancer case and has information on comorbidity, civil status and education level, all of which can be used to increase the comparability in calculation of expected survival. Comorbidity was classified according to four levels of CCI (0, 1, 2 or ≥ 3) and a novel Drug Comorbidity Index (DCI) that predicts an individual's risk of death from any cause based on drug prescriptions the year prior to diagnosis¹⁰⁵. Expected survival was also calculated using comparators one and two years younger than their index case to investigate the size of the incomparability bias in absolute terms.

Paper III

Study design

In the third paper of this thesis, we investigated the amount of evidence in support of prostate cancer as the cause of death in a study sample of 495 men who died of prostate cancer between 2011 and 2018 according to the Cause of Death Register. The study sample included men diagnosed with prostate cancer at 20 selected hospitals in Sweden. The sample procedure is further described in figure 5. Age groups were defined as <70, 70-74, 75-79, 80-84, 85-89, and 90+ and risk category at diagnosis was defined according to a modified NCCN categorization as previously described.

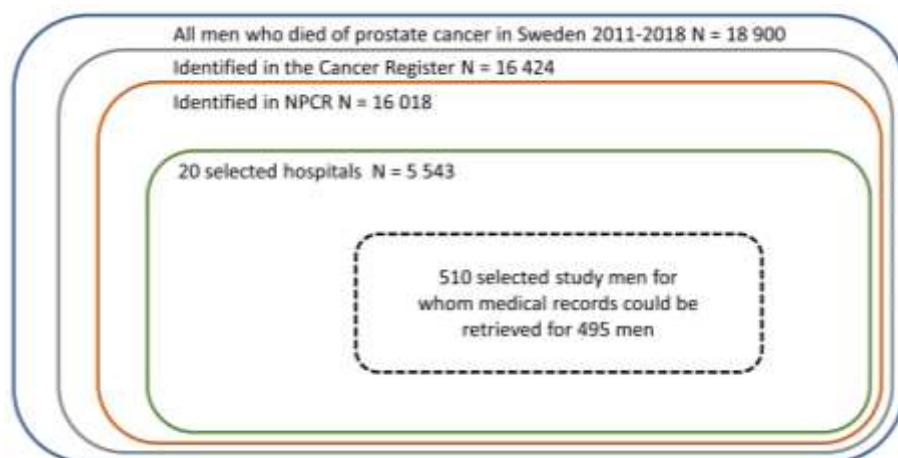


Figure 5. Sampling procedure for 495 study men who died of prostate cancer between 2011-2018 according to the Cause of Death Register.

As shown in table 1, older men and men with low-risk prostate cancer at diagnosis were oversampled to increase estimate precision in these groups¹⁰⁶. Risk groups were sampled proportionally for all age groups to allow for direct comparisons between older and younger men.

Table 1. Sample and stratum sizes for a study sample of 495 men out of 5 543 men in the study frame with stratification on age and risk category, and total number of prostate cancer deaths (shown in parenthesis) between 2011-2018 in NPCR.

	All ages	<70	70-74	75-79	80-84	85-89	90+
	Sample/ Stratum size	Sample/ Stratum size	Sample/ Stratum size	Sample/ Stratum size	Sample/ Stratum size	Sample/ Stratum size	Sample/ Stratum size
All risk categories	495/5543 (16008)	73/748 (1979)	73/731 (2066)	74/941 (2714)	73/1199 (3529)	202/1222 (3582)	0/702 (2138)
Low-risk	162/322 (870)	24/27 (66)	23/43 (89)	25/53 (140)	24/78 (210)	66/73 (228)	0/48 (137)
Intermediate-risk	199/675 (2134)	29/47 (137)	30/67 (211)	30/117 (366)	29/169 (532)	81/177 (567)	0/98 (321)
High-risk	101/1470 (4732)	15/122 (342)	15/130 (462)	15/229 (728)	15/351 (1125)	41/398 (1287)	0/240 (788)
Regional or distant metastases	33/3026 (8086)	5/550 (1421)	5/488 (1291)	4/535 (1451)	5/586 (1616)	14/561 (1455)	0/306 (852)
Missing risk category	0/50 (186)	0/2 (13)	0/3 (13)	0/7 (29)	0/15 (46)	0/13 (45)	0/10 (40)

Staff at each hospital scrutinized all available health care records in search for information in support of prostate cancer as cause of death. Information on prostate cancer progression was filled into a standardized digital form by each extractor (figure 6).

PSA Rapportera sista PSA värde innan död i rad 1, omvänt kronologisk ordning, dvs sista datum först. Om inga värde finns senaste 5 år före död, använd senaste värde (ett värde).

PSA1 (ng/ml)	<input type="text"/>	Datum för PSA1 (AAAAAMDD)	<input type="text"/>
PSA2 (ng/ml)	<input type="text"/>	Datum för PSA2 (AAAAAMDD)	<input type="text"/>
PSA3 (ng/ml)	<input type="text"/>	Datum för PSA3 (AAAAAMDD)	<input type="text"/>
PSA4 (ng/ml)	<input type="text"/>	Datum för PSA4 (AAAAAMDD)	<input type="text"/>
PSA5 (ng/ml)	<input type="text"/>	Datum för PSA5 (AAAAAMDD)	<input type="text"/>

Värdering av metastaser. Om exakt antal metastaser saknas men orden "flera", "multipel" eller "många" beskriver antal metastaser, använd ">3"

Har skelettscintigrafi utförts?	<input type="text"/>	Datum (AAAAAMDD)	<input type="text"/>
		Antal metastaser	<input type="text"/>

Har datortomografi (inkl. PET-CT) utförts?	<input type="text"/>	Datum (AAAAAMDD)	<input type="text"/>
Metastastokal; om metastastas i flera organ, markera dessa organ. Totalt antal metastaser anges		<input type="checkbox"/> Skelett	<input type="checkbox"/> Lymfkörtlar
		<input type="checkbox"/> Mjukdelar	<input type="checkbox"/> Oklart
		Antal metastaser	<input type="text"/>

Endast klinisk värdering av metastaser utfört. Använd om bildundersökning som visar metastaser saknas.

Smärta och terapi

Har patienten haft skelettsmärta sannolikt pga. prostatacancer >3 månader före död?

Har patienten fått regelbunden parenteral smärtmedicin sista tre månaderna före död?

Har patienten under sina tre sista levnadsår behandlats för prostatacancer med:

Cytotatika?	<input type="text"/>	Xoligo (Radium-223)?	<input type="text"/>
Palliativ strålterapi?	<input type="text"/>	Nefrostomi?	<input type="text"/>
Suprapubisk kateter?	<input type="text"/>	Abirateron?	<input type="text"/>
Enzolutamid?	<input type="text"/>	Opial per oralt?	<input type="text"/>
Stöjeläkemedel?	<input type="text"/>		

vilket läkemedel?

Var patientens prostatacancer bedömd som kastrationsresistent?

Figure 6. Standardized digital form used by data extractors to collect evidence in support of prostate cancer as cause of death.

Evidence in support of prostate cancer death included last five measurements of PSA, imaging evidence of metastatic disease and treatment for progressive prostate cancer e.g. Gonadotropin Releasing Hormone (GnRH) agonist or orchidectomy, chemotherapy, Radium-223 or Androgen Receptor Targeted drugs (ARTs).

In order to summarize the level of evidence for prostate cancer death in each men in the study sample we assigned points to each evidence factor as summarized in table 2. The total amount of evidence was classified as: no evidence (0 points), moderate evidence (1 point), strong evidence (2 points) and very strong evidence (3–9).

Table 2. *Factors used to objectively assess the amount of evidence in support of prostate cancer death.*

	Points
PSA > 100 ng/ml	1
PSA doubling time < 6 months ^a	1
Metastasis on imaging ^b	
≤ 3 bone metastasis	2
Visceral metastases or > 3 bone metastasis	3
GnRH or orchidectomy	1
Castration resistant prostate cancer ^c	3

a. Calculated on last two PSA measurements before death. Information on second PSA was missing in 10 men. Last PSA measurement had to be 1 year or less before date of death.

b. Evidence of metastases on imaging including bone scintigraphy, x-ray, computed tomography, positron emission tomography or magnetic resonance imaging.

c. Clinical assessment, PSA ≥ 50 ng/ml on GnRH or use of chemotherapy, androgen receptor targeted drugs or Radium-223

Statistical analysis

The amount of evidence for men in the study sample was described by frequency counts and percentages. Standard statistical methods for stratified sampling were used to estimate the amount of evidence for men in the study frame by percentages with confidence intervals (CIs)¹⁰⁶. Results were analysed by age at death and risk category at diagnosis. To assess if our study sample was representative of all men who died of prostate cancer in NPCR, we compared cancer characteristics for men diagnosed within the 20 selected hospitals with all men in NPCR.

Paper IV

PRISM-PC simulation model

In paper IV we apply the PRISM-PC simulation model to estimate the lifetime risk of prostate cancer in relation to diagnostic activity and life expectancy. The PRISM-PC model parameters were estimated based on Swedish demographic data from the National Board of Health and Welfare, and data on all men diagnosed with prostate cancer between 1992 and 2016 in PCBaSe, as well as their prostate cancer-free comparators, matched on age and region of residence. The model has been described in detail previously^{94,95}. In brief, the model simulates life trajectories for a hypothetical cohort from age 40 to age 100. At each year of follow-up, the model simulates who has been diagnosed with prostate cancer, remained prostate cancer-free, died from prostate cancer, or died from other causes than prostate cancer (figure 7). Age and calendar year-specific incidence of low and intermediate-risk prostate cancer in each of the 21 regions in Sweden is used as a proxy for diagnostic activity in the model. PRISM-PC applies an APC model to calculate age-dependent life expectancy of men without prostate cancer based on the comparators in PCBaSe.

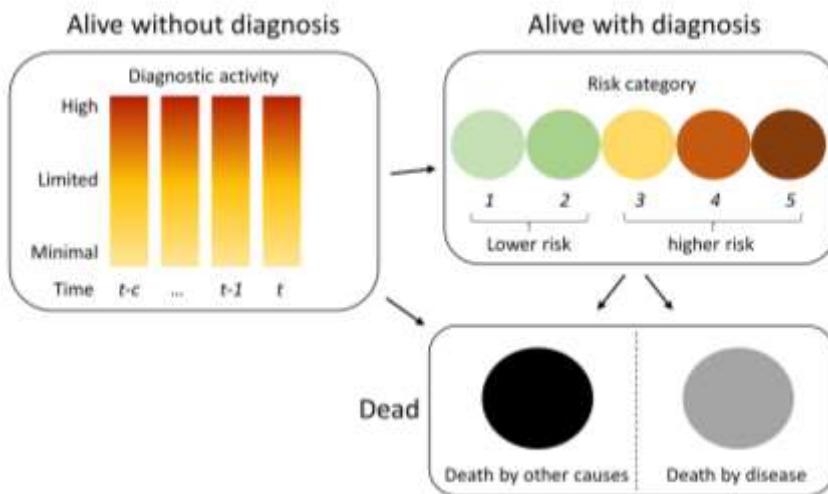


Figure 7. Possible transitions between states at each follow-up year in the PRISM-PC simulation model. Source: Westerberg M, Larsson R, Holmberg L, Stattin P, Garmo H. Simulation model of disease incidence driven by diagnostic activity. *Statistics in medicine*. 2021;40(5):1172-1188.

Study design

Projections were made based on a pre-specified level of the proxy for diagnostic activity for each birth-cohort at each year of follow-up, and a pre-specified level of life-expectancy. These were formulated in terms of age-specific observed levels of the proxy at a particular year, and birthyear-specific risk of death for men without prostate cancer. Model extrapolation was used to project life expectancy between age 40 and 100 outside the time frame 1992-2016. One hundred repeated simulations of lifetime trajectories of a hypothetical cohort of 2 000 000 men was used to estimate the lifetime risk of a prostate cancer diagnosis by three levels of diagnostic activity (figure 8); low as in Sweden 1992, intermediate as in Sweden 2016, and high as in Stockholm 2014 (a year when the Stockholm-3 study invited men to PSA testing¹⁰⁷), and one of three levels of life expectancy; short for men born in 1912, intermediate for men born in 1952 and long for men born in 1992. Lifetime risk of prostate cancer was calculated as the cumulative incidence of prostate cancer by risk category throughout the follow-up period. Point and variance estimates extracted from each simulation were pooled across the 100 simulations for each scenario.

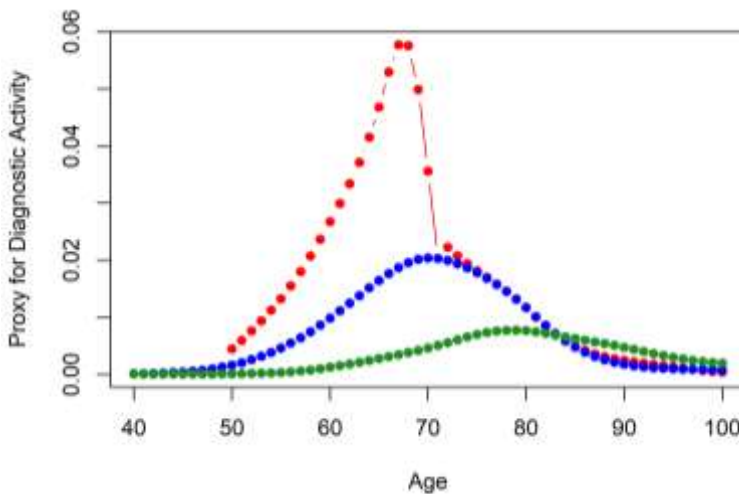


Figure 8. Three levels of the proxy for diagnostic activity; low as in Sweden 1992 (green), intermediate as in Sweden 2016 (blue) and high as in Stockholm 2014 (red).

Ethical considerations

Data collection and registration

NPCR

Data on men diagnosed with prostate cancer has been collected and registered in NPCR since 1998 in Sweden. NPCR, a clinical cancer register, certified by Swedish Association of Local Authorities and Regions (SKR), applies an opt-out procedure, meaning that NPCR does not collect written informed consent by registered men. This is in line with all other clinical cancer registers in Sweden. In all waiting rooms, information on the use and purpose of data collection in NPCR is posted. In addition, staff should inform the men that registration is voluntary and that a man can ask to be excluded from NPCR at any time. Information is also posted at the NPCR website, www.npcr.se, specifically <https://npcr.se/npcr/undersida-2/>.

PCBaSe

For the creation of each iteration of PCBaSe an application to the Regional Research Ethics Board and subsequently Research Ethics Authority has been filed. At the next step, an application is sent to the National Board of Health and Welfare and to Statistics Sweden. There, a review of the application is performed and when the applications have been cleared, linkages are performed. The data and personal identity number for men in NPCR are then transferred to Statistics Sweden (Statistiska centralbyrån; SCB) and the National Board of Health and Welfare (Socialstyrelsen; SoS) where data from other health care registers and demographic databases are added by use of the person identity number. In addition, five control men, matched on birth year and county of residence to the index case, are selected at Statistics Sweden and the person identity number of these men is then sent to SoS and checked against the Cancer Register in order to exclude men that have a diagnosis of prostate cancer. Each case and each control are assigned a unique code number as the sole identifier in files exported outside of Statistics Sweden and the National Board of Health and Welfare. A code key between person identity number and this code is held at SoS in order to allow for subsequent updates that are made in order to extend follow-up.

Risk assessment

The studies of this thesis include previously documented data only i.e. no additional diagnostic or laboratory examinations were performed, and no direct contact was made with the study men. Data in NPCR is regulated by the Patient Data Act (2008) which governs the processing of personal data within health and medical care. The study men are under no risk of physical harm, however, personal integrity is inevitably at risk as in all clinical cancer research. To minimize the risk of violating personal integrity, information on personally identity is only kept by institution with high level of data security. The personal identity number has been replaced and only necessary variables are included in the study files for this thesis. Furthermore, the data is only presented on a group level, not individually. We therefore argue that the scientific value of our research outweighs the minimal risk of violating personal integrity.

Ethical approvals

The Regional Ethical Review Board of Uppsala University approved the studies in this thesis; study I, II and IV: Uppsala Research Ethics Board approval number 2016-239, study III: Research Ethics Authority approval number 2019-02074 and 2019-02695.

Results

Paper I

In total 20 350 men were diagnosed with locally advanced prostate cancer in NPCR between 2000 and 2016. From the first to the last study period, median PSA declined marginally from 24 ng/ml to 20 ng/ml, and the proportion of T4 tumours decreased minimally from 8% to 6%, whereas a strong Gleason grade migration was observed with an increase in GGG 4 and 5 from 27% to 48% (figure 9).

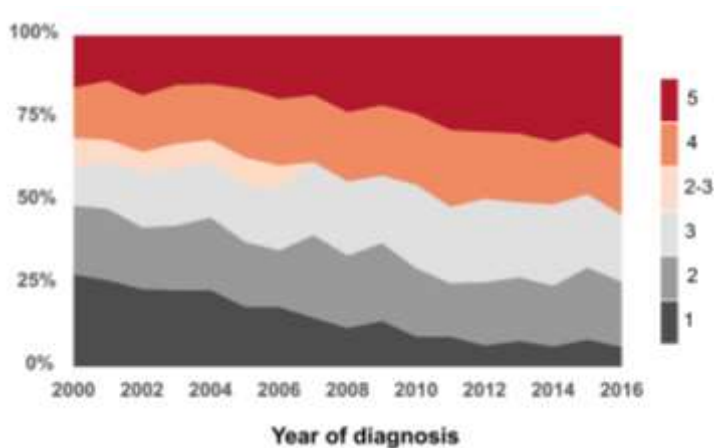


Figure 9. Changes in Gleason Grade Groups in men diagnosed with locally advanced prostate cancer in NPCR between 2000-2016.

The proportion of men below age 80 treated with primary radical treatment almost tripled from 22% to 64% during the study period (figure 10). This increase was mostly due to increase in the use of radiotherapy, from 18% to 48%, and to a lesser extent by increase in radical prostatectomy, from 4% to 15%. Men above age 80 were almost never treated with curative intent (48/6159, <1%).

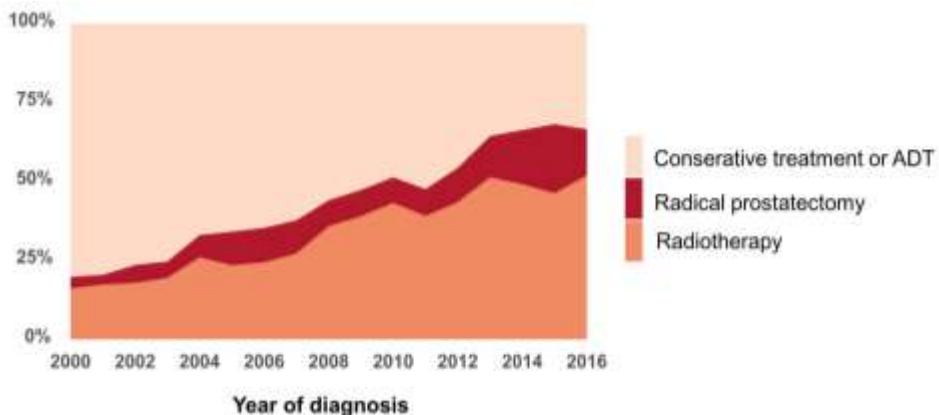


Figure 10. Changes in primary treatment for men age 80 or younger with locally advanced prostate cancer in NPCR between 2000-2016. ADT: Androgen deprivation therapy.

The mode of radiotherapy and radiation dose developed substantially, with increased use of hypofractionated radiotherapy (dose fraction ≥ 2.4 Gy), from 1% to 22%, and increased use of external beam radiotherapy with a total dose of 74 Gy or more, from 20% to 44% (figure 11). Robot-assisted laparoscopic radical prostatectomy mostly replaced the retropubic technique, accounting for 69% of all radical prostatectomies in 2012-2016 (figure 12).

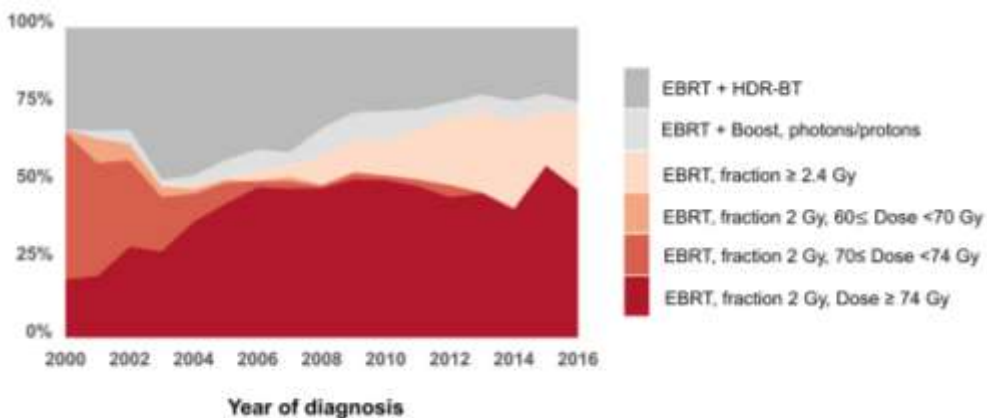


Figure 11. Changes in mode of radiotherapy and radiation dose for men with locally advanced prostate cancer in NPCR between 2000-2016. EBRT: External beam radiation therapy, HDR-BT: High-dose-rate brachytherapy.

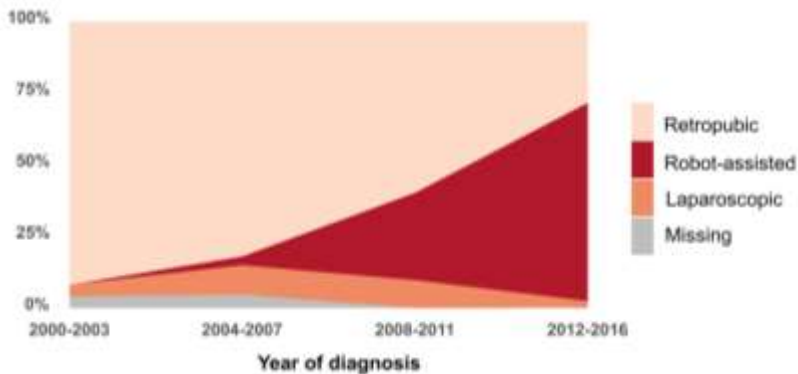


Figure 12. Changes in operation type for men operated with radical prostatectomy for locally advanced prostate cancer in NPCR between 2000-2016.

The cumulative incidence of prostate cancer death for all men below age 80 with locally advanced prostate cancer, including men who received conservative treatment, declined from 17% to 10% from the first to the last study period. In men between ages 65 and 74, mortality declined by 50%, or from 16% to 8%, whereas mortality remained unchanged in men age 85 or older, or 30% vs. 32%.

As the numbers above present, we estimated the cumulative incidence of prostate cancer death in this paper, considering other causes of death as competing risk events. This is commonly used to present risk of prostate cancer death as it gives a more realistic measure of the actual risk of dying of prostate cancer since most men with prostate cancer will die from other causes. Later, after publishing, we realized that cumulative mortality using the Kaplan-Meier method would have been more appropriate in this setting, since the aim was to compare different time periods. This would allow us to compare the time periods independently of changes in competing risk. The difference between cumulative mortality assessed by the cumulative incidence method and the Kaplan-Meier method is demonstrated in Figure 13. Using the Kaplan-Meier method, cumulative prostate cancer mortality for all men below age 80 declined from 19% to 11% during the study period, whereas for men between ages 65 and 74 cumulative prostate cancer mortality declined from 17% to 8%. For men age 85 or older, the mortality remained unchanged, 43% vs. 45%. The effect of censoring competing events is therefore marginal in men below age 80 whereas the effect is substantial in men 85 or older.

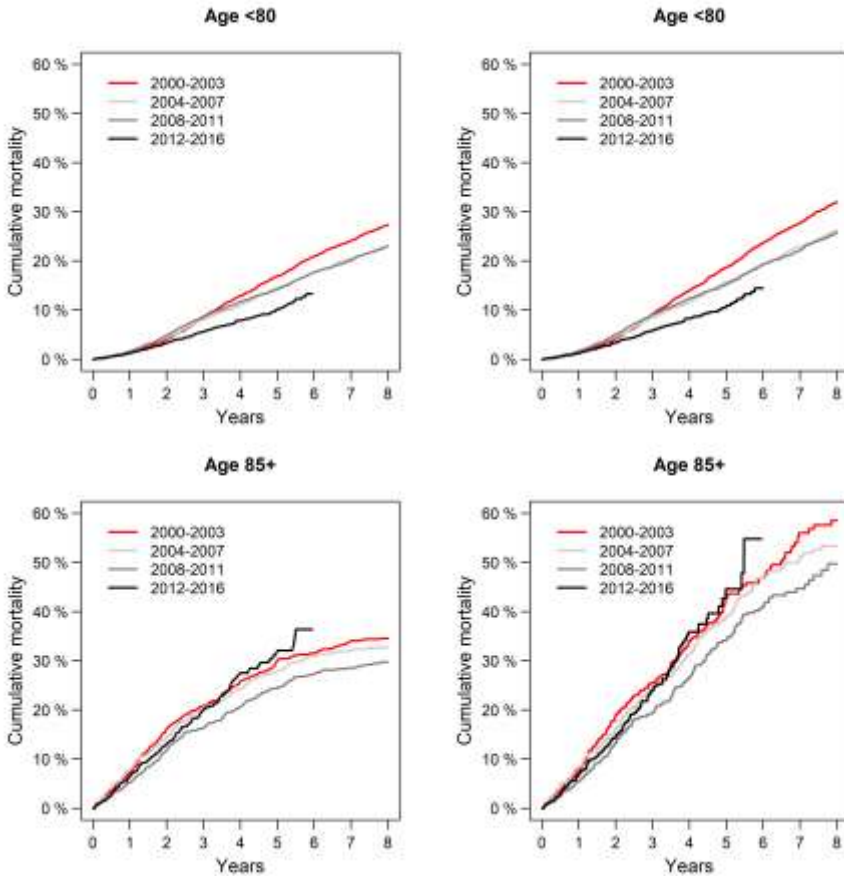


Figure 13. Cumulative prostate cancer mortality for men with locally advanced prostate cancer between 2000-2016. Competing risks of death accounted for (left) or censored (right).

The hazard of prostate cancer death associated with the use of radical treatment was estimated using calendar periods as a proxy for radical treatment (figure 14). After adjusting for other period-related changes such as age, PSA levels, T and M stage, CCI, civil status, and educational level, men age 80 or younger diagnosed between 2012-2016 had a lower hazard of prostate cancer death compared to men diagnosed in 2000-2003, hazard ratio (HR) 0.65 (95% CI 0.56-0.76). Additional adjustment for radical treatment eliminated most of the residual hazard between calendar periods, HR 0.89 (95% CI 0.76-1.05).

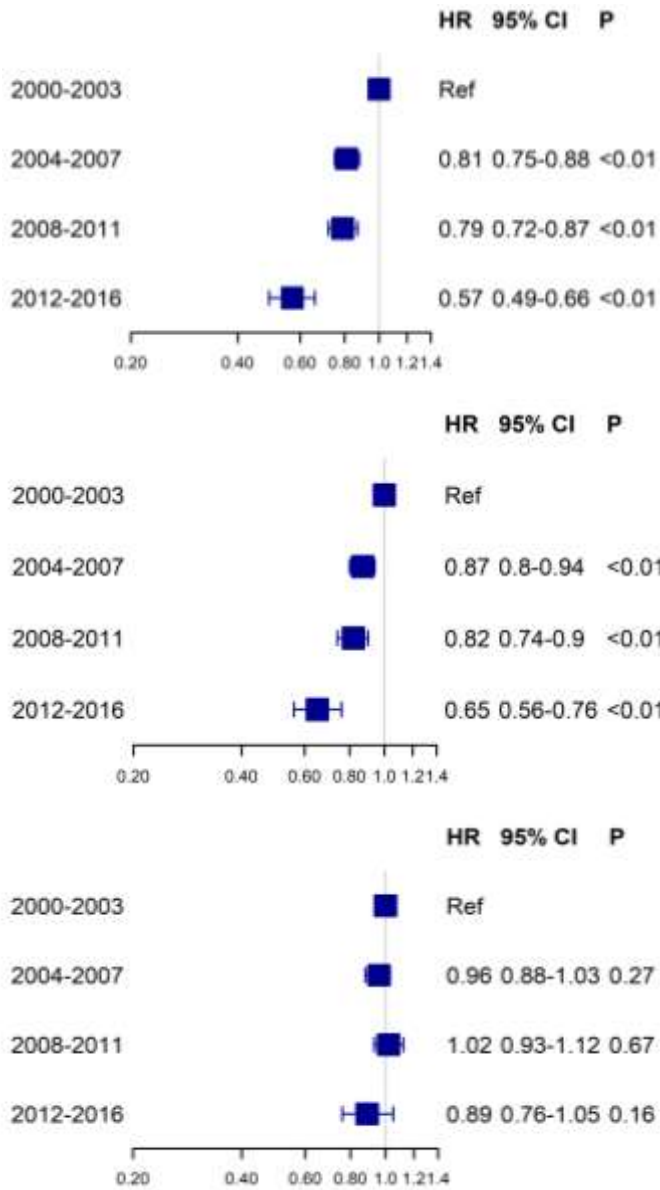


Figure 14. Cox regression analysis of the hazard of prostate cancer death by calendar period, unadjusted (top) and after adjusting for age, PSA, T and M stage, CCI, civil status and educational level (middle), and additionally adjusting for radical treatment (bottom).

There were large geographical differences in the use of radical therapy and prostate cancer mortality during the later half of the study period (figure 15). The use of radical treatment was lowest in Östergötland region; 44%, and highest in Västerbotten region; 73%. At the same time prostate cancer mortality varied from 7% to 19% between regions.

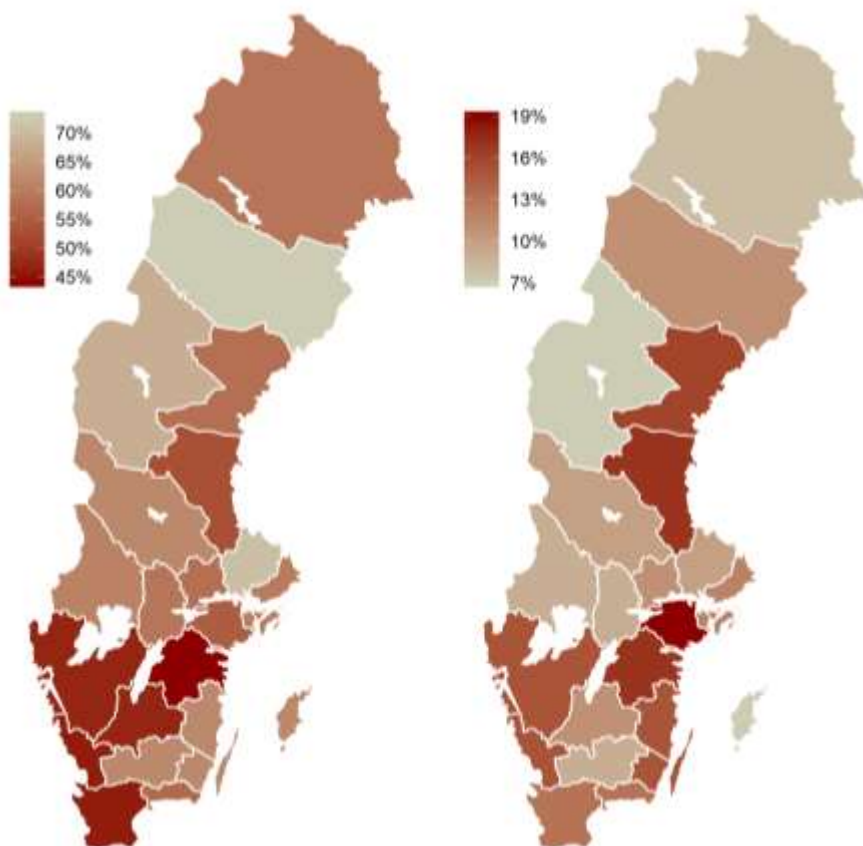


Figure 15. Local variations in the use of radical treatment (left) and 5-year cumulative incidence of prostate cancer mortality (right) for men with locally advanced prostate cancer in Sweden 2008-2016.

Paper II

In total 168 793 men below age 90 were diagnosed with prostate cancer in NPCR between 2000 and 2016, of which 90 432 or 54% had low or intermediate-risk prostate cancer. Relative survival was higher than cause-specific survival for the whole cohort, both at five years after diagnosis, 90% vs. 87% and at 10 years, 85% vs. 77%.

There were large differences in 5-year relative and cause-specific survival for men above age 80, in particular for low-risk prostate cancer, or 116% (95% CI 112-121%) vs. 96% (95% CI 95-97%), and intermediate-risk prostate cancer, 112% (95% CI 109-115%) vs. 92% (95% CI 91-93%), and to a lesser degree for high-risk prostate cancer, 88% (95% CI 86-90%) vs. 76% (95% CI 75-77%) (figure 16). This difference continued to increase at 10 years for men with low or intermediate-risk prostate cancer. In contrast, men in all age groups with regional or distant metastases at diagnosis had similar relative and cause-specific survival, with a difference of 3% or less between estimates.

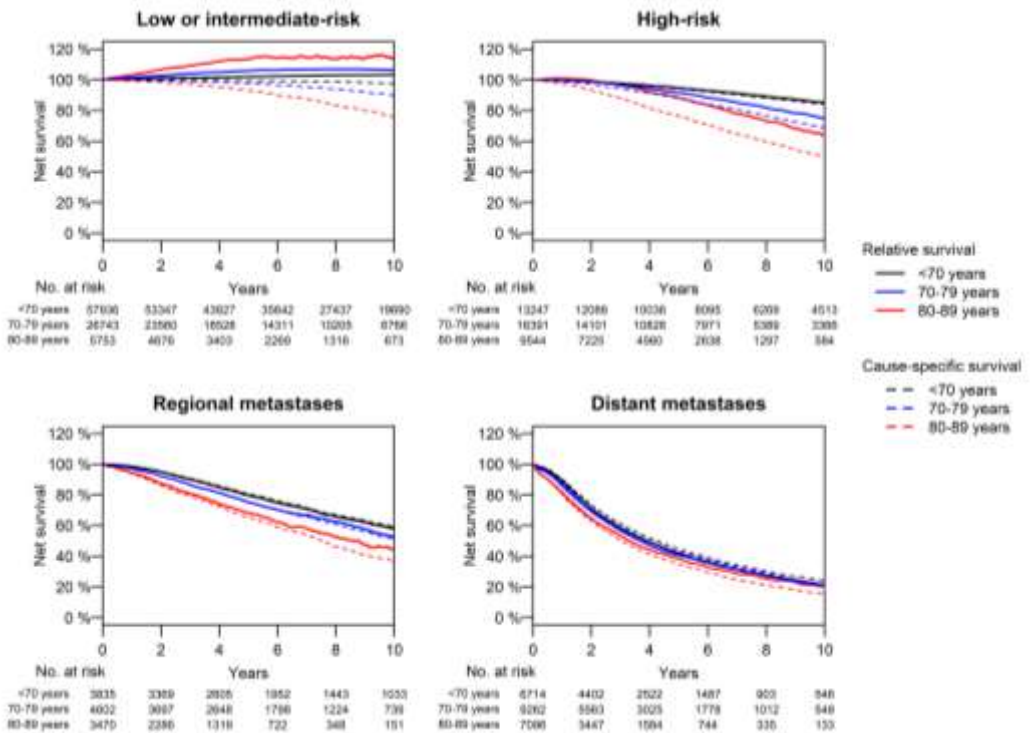


Figure 16. Relative and cause-specific survival by age and risk category in men diagnosed with prostate cancer in NPCR between 1998-2016.

The fact that relative survival was well above 100% for men age 80 or older with low or intermediate-risk prostate cancer suggests that these men are healthier than men in the general population of the same age and birthyear. In order to overcome this incomparability bias in expected survival, we additionally matched men above age 80 on comorbidity, civil status and educational level using comparators in PCBaSe. This resulted in a decrease in the relative survival for men above age 80 with low or intermediate-risk prostate cancer, from 116% to 106% at five years and 120% to 104% at 10 years (top graph in figure 17). Additional matching did not substantially affect the relative survival of men with regional or distant metastases.

To understand what this decrease in relative survival translates to in more absolute terms, relative survival for men above age 80 with low or intermediate-risk prostate cancer was estimated using comparators one year younger than their index case matched by calendar year only (figure 17). This resulted in a similar relative survival as the fully matched analysis i.e. by same age, calendar year, comorbidity, civil status and educational level. Men above age 80 with low or intermediate-risk prostate cancer are therefore in a biological sense at least one year younger than men of the same age in the general population. The analysis was repeated with comparators two years younger than the index case, and this further decreased the relative survival of men above age 80 with low or intermediate-risk prostate cancer, however, relative survival remained higher than cause-specific survival for these men.

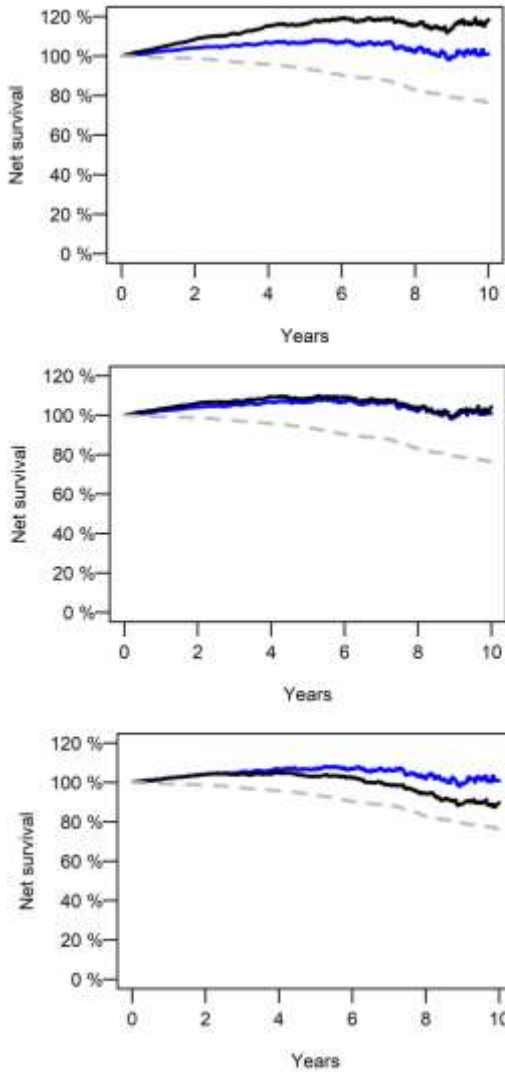


Figure 17. Relative survival (black line) for men age 80-89 with low or intermediate-risk prostate cancer in NPCR between 2007-2016 with comparators matched by calendar year and same age (top), one year younger (middle) or two years younger (bottom) than their index case. Relative survival (blue line) with comparators matched by same age, calendar year, comorbidity, civil status and educational level. Cause-specific survival shown in gray.

Paper III

Evidence in support of prostate cancer as cause of death was analysed in 495 men who died of prostate cancer according to the Cause of Death Register. Older compared to younger men had more often no or moderate evidence of prostate cancer as cause of death, 29% vs. 14% (Table 3, figure 18). In younger men the proportion of no or moderate evidence decreased with increasing risk category; 21% for low-risk, 14% for intermediate-risk, 8% for high-risk, and 0% for regional or distant metastases. In contrast, the proportion of no or moderate evidence was similar between risk categories in older men, 31% for low-risk, 29% for intermediate-risk, 29% for high-risk and 21% for regional or distant metastases.

Table 3. Amount of evidence in support of prostate cancer death for the 495 men in the sample who died of prostate cancer according to the Cause of Death Register during 2011-2018.

Age	No evidence 0 points		Moderate evidence 1 point		Strong evidence 2 points		Very strong evidence ≥3 points	
	n	%	n	%	n	%	n	%
<85 years								
All	30	10	11	4	3	1	249	85
Low-risk	18	19	2	2	2	2	74	77
Intermediate-risk	9	8	7	6	1	1	101	86
High-risk	3	5	2	3	0	0	55	92
Regional or distant metastases	0	0	0	0	0	0	19	100
85–89 years								
All	28	14	30	15	3	1	141	70
Low-risk	11	17	9	14	1	2	45	68
Intermediate-risk	12	15	11	14	1	1	57	70
High-risk	5	12	7	17	1	2	28	68
Regional or distant metastases	0	0	3	21	0	0	11	79

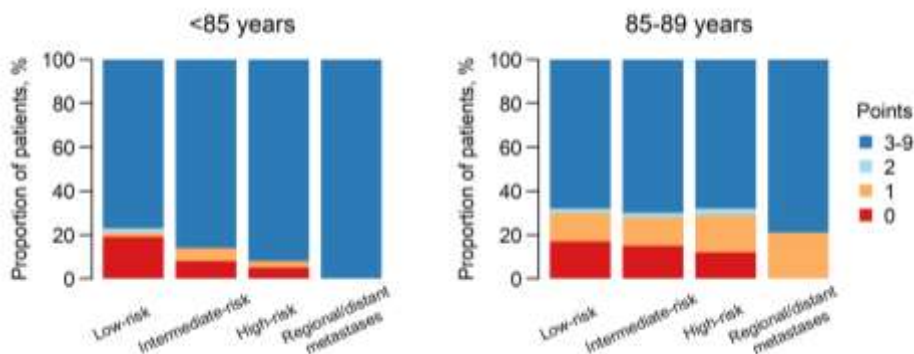


Figure 18. Amount of evidence in support of prostate cancer death for the 495 men in the sample who died of prostate cancer according to the Cause of Death Register during 2011-2018.

The results of the analysis of the study sample ($n = 495$) were weighted according to techniques of stratified sampling to estimate the amount of evidence in support of prostate cancer as cause of death for all men in the study frame ($n = 5\,543$). In total, 13% had no or moderate evidence of prostate cancer death. Around 35% of the study frame was 85 years or older at time of death, and out of these 25% had no or moderate evidence of prostate cancer death. Only 6% of the study frame had low-risk prostate cancer at diagnosis and out of these 24% had no or moderate evidence of prostate cancer death.

Men diagnosed at the 20 selected hospitals for the study frame had similar distribution of age, PSA levels and risk categories at diagnosis as all men diagnosed in NPCR; median age 70 in both groups, median PSA 10 vs. 11 ng/ml, and the proportion of low or intermediate-risk prostate cancer, 51% vs. 54%.

Paper IV

Results of the simulation show that higher diagnostic activity increased the lifetime risk of prostate cancer diagnosis overall, 18% for low activity, 21% for intermediate activity, and 29% for high diagnostic activity, using long life expectancy in all scenarios. Men exposed to high diagnostic activity had, compared with men exposed to low diagnostic activity, a five-fold higher lifetime risk of low or intermediate-risk prostate cancer, 22% vs. 5%, or 1 in 4 men vs. 1 in 22 men, and half the risk of high-risk or metastatic prostate cancer, 6% vs. 13%, or 1 in 16 vs. 1 in 8 men (figure 19).

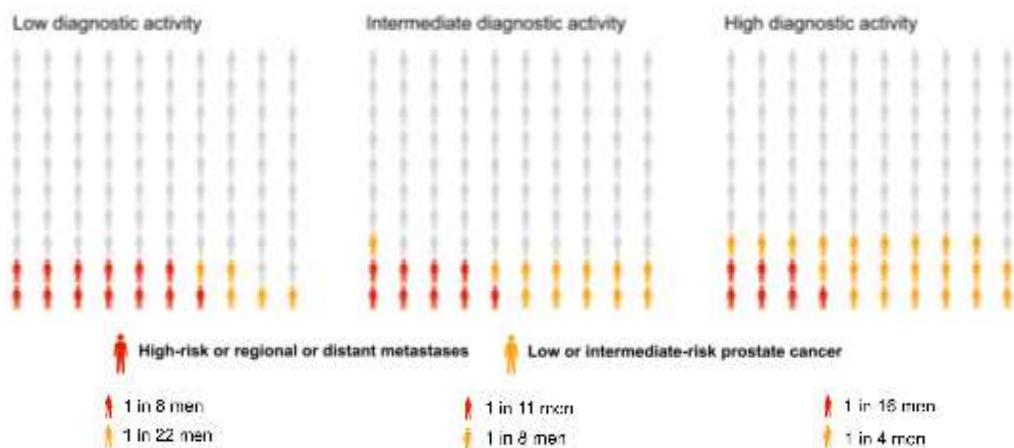


Figure 19. Lifetime risk of a prostate cancer diagnosis by risk category under three levels of diagnostic activity; low as in Sweden 1992, intermediate as in Sweden 2016, and high as in Stockholm 2014 (when the Stockholm-3 study invited men to measure their PSA¹⁰⁷).

Long life expectancy modestly increased the lifetime risk of prostate cancer overall, 15% for short life expectancy, 18% for intermediate and 21% for long life expectancy, using the intermediate diagnostic activity in all scenarios. Men with long life expectancy had, compared with men with short life expectancy, a higher lifetime risk of prostate cancer in all separate risk categories, especially for high-risk or metastatic prostate cancer, 9% vs. 5%, or 1 in 11 men vs. 1 in 19 men (figure 20).

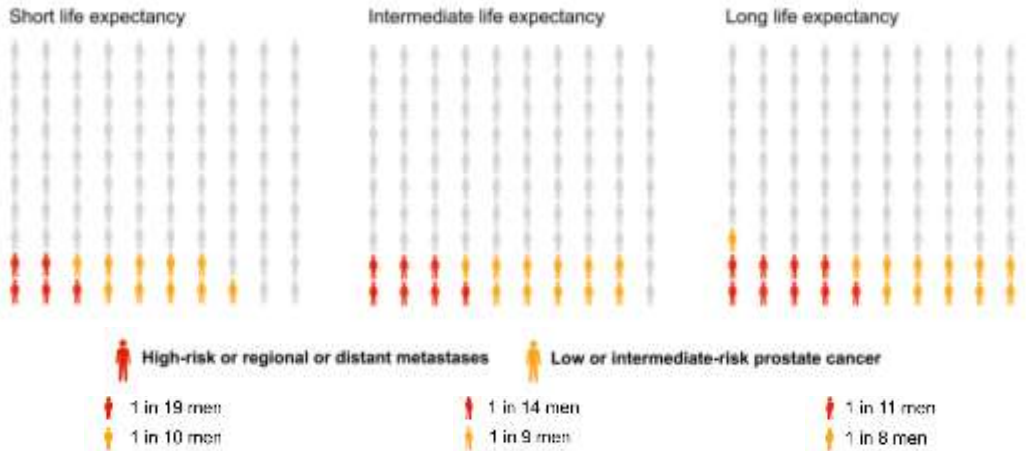


Figure 20. Lifetime risk of a prostate cancer diagnosis by risk category under three levels of life expectancy; short as for birth cohort 1912, intermediate as for birth cohort 1952, and long as for birth cohort 1992.

For every scenario of diagnostic activity and life expectancy, lifetime risk of prostate cancer increased marginally from age 80 to age 100, except for men with long life expectancy, for whom lifetime risk of distant metastases doubled for every level of diagnostic activity (table 4).

Table 4. Lifetime-risk of prostate cancer overall and per risk category according to life expectancy for three birth cohorts, applying intermediate diagnostic activity in all scenarios. Results shown for follow-up at age 80 and age 100.

Risk category	Short Birth year 1912		Intermediate Birth year 1952		Long Birth year 1992	
	80 y %	100 y %	80 y %	100 y %	80 y %	100 y %
All	13.2	14.7	15.3	18.4	16.6	21.4
Low-risk	3.7	3.8	4.2	4.4	4.5	4.8
Intermediate-risk	5.4	5.7	6.2	6.8	6.7	7.5
High-risk	2.3	2.7	2.7	3.7	3	4.4
Regional metastases	0.7	1	0.9	1.4	1	1.7
Distant metastases	1.1	1.5	1.3	2.3	1.4	3
Low or intermediate-risk	9.1	9.5	10.4	11.2	11.2	12.3
High-risk or regional or distant metastases	4.1	5.2	4.9	7.3	5.4	9.1

Discussion

Paper I

In the first paper we studied whether increased use of radical treatment for men with locally advanced prostate cancer has led to a decrease in prostate cancer mortality for Swedish men. The use of radical treatment in men below age 80 almost tripled from the first to the last calendar period. This trend was even noticeable to some extent before results from randomized trials were published^{44,45}. During the same time period, prostate cancer mortality almost halved in men below age 80.

A direct causality between the use of radical treatment and lower mortality is difficult to prove in an observational setting due to risk of confounding by indication of treatment e.g. men with non-favourable cancer characteristics and high frailty may be less likely to receive treatment if they are not expected to benefit from or tolerate the treatment¹⁰⁸.

To limit confounding by indication of treatment we assessed the hazard of death according to calendar period as a proxy for treatment intensity. Despite adjusting for multiple temporal factors in the regression model, apart from radical treatment, the hazard of prostate cancer death remained lower in the last calendar period. This residual hazard was largely eliminated after additionally adjusting for treatment, indicating that increased use of radical treatment is to a large extent accountable for the decrease in prostate cancer mortality observed in our study.

There are a few time-dependent aspects that need to be discussed further. In later periods most men with locally advanced prostate cancer underwent bone imaging while in earlier periods men were selected for bone imaging according to their overall health status. Limiting our analysis to men with M0 disease would exclude men with poor health status in earlier time periods and bias the analysis. Due to increased use of bone imaging, the proportion of men with Mx status decreased from 57% in the first period to 38% in the last. Including Mx status may therefore also bias our analysis since the first period includes more men with unknown metastases and poor survival. To limit this confounding, we adjusted for Mx and M0 status in the regression analysis. All N stages were included in our study since the indication for staging changed during the study period. In the first periods results from pathological staging of lymph nodes were mainly obtained from pelvic lymphadenectomy, performed as a staging procedure before radiotherapy in high-risk men,

whereas in later periods lymphadenectomy was often performed concomitantly with prostatectomy. Furthermore, the prevalence of positive nodes at surgical lymph node staging was affected by increased use and development of non-invasive diagnostic imaging during the study period i.e. men with obvious lymph node metastases at imaging would not undergo surgical staging. In a sensitivity analysis, excluding men with Mx status or N1 status from the analysis did not alter our main results.

Changes in the ISUP classification system in 2005 resulted in a grade migration in GGGs e.g. men in earlier periods were more likely to be graded with GGG 1, whereas men with similar kind of histology characteristics were graded as GGG 2 in later periods. Therefore, GGG was excluded from the regression analysis since this would overestimate survival in later periods.

The use of chemotherapy for men with metastatic prostate cancer increased during the study period after docetaxel emerged in 2004¹⁰⁹. Around half of all men below age 80 who died of prostate cancer in Sweden between 2009-2010 received chemotherapy¹¹⁰. Advancements in treatment of metastatic prostate cancer may have contributed to lower mortality in later periods in our study. This is supported by evidence of improved survival in men with de-novo metastatic prostate cancer during the last two decades in Sweden¹¹¹.

In the last calendar period, radiotherapy was still the main treatment modality for men with locally advanced prostate cancer. The proportion of men who received a total radiotherapy dose of 74 Gy or more doubled during the study period, which has been proven beneficial for prostate cancer survival in several randomized trials^{112,113}. The use of hypofractionated radiotherapy (≥ 2.4 Gy) has increased and accounted for one in every four radiotherapy treatments in the last study period. Higher radiation fractions enable shorter treatment duration and have been proven non-inferior to conventional fractions in terms of biochemical failure-free survival and late term toxicity¹¹⁴⁻¹¹⁶. External beam radiotherapy combined with high-dose-rate brachytherapy for men with high-risk prostate cancer has lately shown promising results in recent observational series^{117,118}.

The use of radical prostatectomy tripled during the study period, accounting for around a fourth of all radical treatments in the last period. There is no evidence available from randomized trials comparing the efficacy of radical prostatectomy to radiotherapy or ADT only for men with locally advanced prostate cancer. Current evidence is based on multiple retrospective observational series and shows comparable overall and cause-specific survival compared with radiotherapy^{52,53}. The SPCG-15 trial is currently recruiting and aims to compare survival outcomes after radical prostatectomy and radiotherapy with ADT⁵⁴. According to guidelines of the European Association of Urology, radical prostatectomy should be considered for selected patients as a part of multi-modal therapy¹¹⁹. Prior extended pelvic lymph node dissection is usually performed and if pN1 disease is confirmed, adjuvant radiotherapy

and long-term ADT is recommended in men with multiple adverse pathological features^{119,120}. In our study around a third received adjuvant or salvage radiotherapy after radical prostatectomy. Three trials are currently underway comparing adjuvant radiotherapy to salvage radiotherapy¹²¹⁻¹²³. Early results on progression free survival have only been published and do not show any significant difference between treatment groups, suggesting that salvage radiotherapy should be favored.

Large geographical variations were noticeable in both the use of radical treatment and in prostate cancer mortality during the study period. Another study based on data from PCBaSe utilized this variation in order to estimate the effect of radical treatment on prostate cancer mortality in men with very high-risk prostate cancer¹²⁴. Instead of using calendar period as in our study, each treatment unit represented different levels of treatment intensity. Men treated at units with high proportion of radical treatment had lower prostate cancer mortality, which is in line with our results.

In this study we show that results from previous randomized trials are also applicable on a population level. Although randomized trials do not suffer from bias related to the indication of treatment, stringent inclusion criteria may affect the generalisability of results. Real-world data from high quality registries are therefore an important compliment to randomized trials and reflect routine clinical practice on a population level.

Paper II

In this paper we compared the relative and cause-specific framework to assess net survival in men with prostate cancer. As in previous studies, relative survival for the whole study population was higher compared with cause-specific survival^{62,63,67,68}. This difference was primarily seen in men with low and intermediate-risk prostate cancer, whereas both methods estimate roughly the same net survival in men with metastatic disease.

Relative survival at five and 10 years was well above 100% in men with low or intermediate-risk prostate cancer, indicating that these men are overall healthier compared with the general population. This may be explained by the fact that men with health-seeking behavior and men with higher socioeconomic status are more likely to be diagnosed with prostate cancer in earlier stages^{125,126}. The comparability bias was more prevalent in men above age 80, since without clinical signs of advanced prostate cancer, old men rarely undergo biopsy of the prostate, unless considered particularly fit.

To increase the comparability, we used comparators in PCBaSe to calculate expected survival for men age 80 or older. This additional matching on comorbidity, social status and educational level decreased the relative survival substantially, however, the estimate remained above 100%. The ex-

pected survival in old men with prostate cancer is therefore still underestimated, indicating that residual bias exists i.e. old men with low-risk or intermediate prostate cancer seem to be a selection of exceptionally healthy men compared to men of the same age in the general population. Interpretation of a relative survival estimate above 100% is limited; one can only conclude that death due to prostate cancer in these men does not counterbalance the healthy screening effect.

In men with low or intermediate-risk prostate cancer, cause-specific survival was substantially lower for older compared to younger men. To some degree this could be explained by the fact that older men are more likely to undergo watchful waiting rather than active surveillance or radical treatment. In a study from NPCR around a third of men under active surveillance received deferred radical treatment¹²⁷. Another explanation could be that prostate cancer is overattributed as the cause of death i.e. old men might be at higher risk of receiving prostate cancer as cause of death despite no evidence of prostate cancer progression⁶⁴. The difference between relative and cause-specific survival continued to increase with time since diagnosis, which could reflect increased difficulties in ascertaining the correct cause of death as the patient ages and more comorbidities arise.

Men with regional or distant metastases at diagnosis had similar net survival in both frameworks. Misclassification errors in death certification are less likely to occur in these men since many will die from the disease in the first few years after diagnosis. Furthermore, men who present with symptoms of local progression or metastases will undergo prostate biopsy even if they are frail. These men are therefore likely more representable of the general population compared to men with low-risk disease.

Net survival is an important measure to assess cancer management and prognosis. The choice of framework to estimate net survival depends on the population and disease under study. Cause-specific survival is more appropriate in a trial setting or subgroup analysis. Relative survival is preferred in population-based studies if the population of interest is representable of the general population or if reliability of death certificates is poor. In old men with low or intermediate-risk prostate cancer, both methods are subject to biases that drives the estimate of net survival in opposite directions. Net survival in these men should be interpreted with care.

Paper III

In paper III we investigated the amount of evidence in support of prostate cancer as cause of death in men who died of prostate cancer according to the Cause of Death Register. Our results show that older men and men with low-risk prostate cancer at diagnosis have less evidence in support of prostate

cancer progression before death compared with younger men and men with high-risk or metastatic prostate cancer at diagnosis.

Results from paper II showed that older compared to younger men with low or intermediate-risk prostate cancer had substantially lower cause-specific mortality. This could in part be explained by our findings in paper III i.e. that the adjudication of prostate cancer death is based on limited evidence for one in every four men who die at age 85 or older. In the absence of strong evidence of prostate cancer progression, prostate cancer as cause of death may be difficult to ascertain and is subject to sticky-diagnosis bias.

Out of all men in our study frame ($n = 5\,543$), 13% were estimated to have no or moderate evidence in support of prostate cancer death. This does not necessarily mean that all men without sufficient evidence of prostate cancer progression died of other causes than prostate cancer. Old men are less likely to be thoroughly followed-up, especially men with stable disease status, and eventual progression in some of these men might not be documented. Our results also do not prove that all men with strong evidence of prostate cancer progression died of prostate cancer. Although less likely, men with signs of progression may also suffer from erroneous adjudication of prostate cancer as cause of death e.g. deaths due to cardiovascular disease or other cancers. In such instances, the progression of prostate cancer may have been a contributing cause. Furthermore, misclassification errors can also cause an erroneous adjudication of other causes of death i.e. when the underlying cause of death was truly prostate cancer but was attributed to another cause. For example, death related to prostate cancer treatment might not be documented as death due to prostate cancer.

Several studies have found high correlation between medical review and death certificates in men with prostate cancer^{80,81}. However, in the study by Penson et al., only men who died in hospital were included for review⁸¹. These men are likely to have more evidence on events leading to death compared to men who die in a nursery or at home. According to the study only a third of all men who died of prostate cancer in the region died in hospital.

In a previous study from the South-East region of Sweden, the reliability of death certificates among young men was high after review of medical records⁶⁴. Nevertheless and consistent with our findings, men with localized disease at diagnosis and men age 75 or older had around 5% excess prostate cancer deaths after medical review compared with official death certificates and this trend increased in later periods of the study. In a more recent study from Norway, a third of prostate cancer deaths were considered over-reported after expert committee review, whereas over-reporting of other cause of death in men with prostate cancer was substantially lower⁶⁵. The proportion of misclassified prostate cancer death exceeded 60% in men age 90 or older and increased with lower Gleason score at diagnosis.

Autopsy is considered the gold standard to verify cause of death. The autopsy rate in Sweden has declined from 49% in 1970 to 11% in 2016¹²⁸. At

very old age i.e. the age when most people die, autopsy rates declined to less than 1%. The decline in autopsies may affect the quality of the Swedish Cause of Death Register negatively, since clinically significant diagnosis may be missing in more than half of all cases where autopsy is not performed¹²⁹.

Automated classification software has been used to improve and standardize the electronic coding of death certificates in Sweden since 1987⁷⁵. The underlying cause of death by manual certification differs from the automated certification in about 20% of the cases⁷⁶. In a study from Norway, manual compared with automated coding of underlying cause of death in men with a prostate cancer diagnosis did not result in significant changes in prostate cancer mortality statistics¹³⁰.

In the last two decades increased diagnostic activity has led to an increase in men with low and intermediate-risk prostate cancer in Sweden, and at the same time life expectancy has increased^{131,132}. In 2020 around 41% (921/2243) of all men who died of prostate cancer were 85 years or older. This has important implications for prostate cancer mortality statistics, since the beneficial effect of earlier diagnosis could in part be masked by an increase in erroneous adjudication of prostate cancer deaths in old men and men with low-risk disease at diagnosis.

Paper IV

In the final paper of this thesis, we studied the lifetime risk of a prostate cancer diagnosis in relation to diagnostic activity and life expectancy. Our results show that high compared to low diagnostic activity increases the lifetime risk of low or intermediate-risk prostate cancer five-fold and halves the risk of high-risk or metastatic prostate cancer. Long life expectancy increased the lifetime risk of prostate cancer modestly in all risk categories.

It is important to mention that our results do not prove the efficacy of a screening program. A decline in metastatic disease at presentation with higher diagnostic activity could simply reflect lead time due to earlier diagnosis. The efficacy of screening is dependent on the efficacy of prostate cancer treatment in screened men that would have presented with metastatic disease later in life.

High diagnostic activity increased lifetime risk of low or intermediate-risk prostate cancer, which not only reflects earlier diagnosis but also increased detection of indolent tumors. Undiagnosed low-risk prostate cancer is very common in old men and most of these men will die with but not from prostate cancer⁴. Lifetime risk of prostate cancer overall is greatly affected by how many low-risk prostate cancers are detected. Therefore, lifetime risk of prostate cancer should preferably be presented per risk category, rather than overall, and the focus should be on the lifetime risk of clinically significant prostate cancer i.e. high-risk and metastatic disease.

Long life expectancy increased lifetime risk of prostate cancer overall modestly, including low and intermediate-risk prostate cancer, and substantially increased the risk of metastatic prostate cancer. This is likely explained by that fact that older men are unlikely to be screened for prostate cancer and are more likely to be diagnosed with symptomatic, advanced disease.

Disease incidence, reported as the number of new cases per 100 000 person-years, is an important measure to describe population-based disease burden as well as to compare different populations and time periods. However, incidence is not an intuitive measure and is not useful for informing patients on disease risk. In contrast, lifetime risk is well-suited for informing laymen and is commonly used by health care providers and media.

Current estimates of lifetime risk of prostate cancer are based on cross-sectional data of current incidence and mortality statistics. Lifetime risk of prostate cancer will continue to evolve since intensity of diagnostic activity and diagnostic accuracy, as well as life expectancy will continue to change. For example, prostate imaging by use of mpMRI has recently become the first step in the diagnostic workup in men with moderately elevated PSA. This will likely decrease the incidence of low-risk prostate cancer if only visible foci are biopsied, since low-risk prostate cancer is rarely visible on mpMRI. This will ultimately lead to a decrease in the lifetime risk of a prostate cancer overall.

Conclusions

- I. The use of radical treatment in men with locally advanced prostate cancer has tripled in the last two decades in Sweden, and this has contributed to a decrease in prostate cancer mortality in all men with locally advanced prostate cancer. Our results indicate that the effects of radical treatment on prostate cancer death observed in randomized trials can also be obtained in a real-world setting or clinical practice.
- II. Net survival in older men with low or intermediate-risk prostate cancer is overestimated in the relative framework since these men are on average healthier than the general population. This bias remained despite efforts to increase the comparability of expected survival. Cause-specific survival was unrealistically low in older compared to younger men with low or intermediate-risk prostate cancer.
- III. Older men and men with low or intermediate-risk prostate cancer at diagnosis, had less evidence in support of prostate cancer as cause of death compared with younger men or men with high-risk or metastatic prostate cancer at diagnosis. Lack of evidence in support of prostate cancer death in these men indicates over-reporting of prostate cancer as cause of death, that may affect prostate cancer mortality statistics.
- IV. The lifetime risk of prostate cancer is highly influenced by level of diagnostic activity and to a less extent by life expectancy. High compared to low diagnostic activity increased lifetime risk of low or intermediate-risk prostate cancer five-fold and halved the risk of high-risk and metastatic prostate cancer, whereas long life expectancy modestly increased the risk of prostate cancer in all risk categories.

Future perspectives

In Sweden more than 100 000 men, or 2% of all men, were living with prostate cancer in 2016⁷. According to projections, the Swedish population is expected to reach 11 million by 2028, with a 50% increase in men age 80 and older¹³³. This will increase incidence and prevalence even more and further increase the importance of prostate cancer management.

The management of locally advanced cancer has largely evolved in the past decades with increased use of radical treatment as a part of multimodal therapy. Treatment remains challenging due to higher risk of biochemical relapse and higher treatment-related comorbidity compared with treatment of organ-confined disease. The benefit of radiotherapy with adjuvant ADT as primary treatment in these men is unquestionable, however, the role of radical prostatectomy is still unclear. To shed light on this uncertainty, the SPCG-15 trial has been recruiting since 2014 and aims to compare radical prostatectomy to radiotherapy in men with T3 disease⁵⁴.

Although the use of radical treatment has substantially increased in Sweden, the question remains if an even higher treatment intensity would further decrease prostate cancer mortality on a population level. A certain proportion of men will always be ineligible for radical treatment due to comorbidity and short life expectancy, however, previous evidence indicates that men in their seventies with high-risk prostate cancer may be undertreated¹³⁴. With an aging population, focus on biological age rather than chronological age is ever more important.

Recently, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has shown superior accuracy in detecting distant metastases in men with high-risk prostate cancer compared to conventional imaging with bone scintigraphy and computed tomography¹³⁵. The role of PSMA PET/CT in the management of men with high-risk prostate cancer in clinical practice is yet to be determined since the effect of more accurate staging on outcome such as death and biochemical relapse requires longer follow-up.

The management of hormone sensitive metastatic prostate cancer has largely evolved in the last decade with more focus on aggressive primary treatment i.e. combining ADT with androgen receptor targeted drugs and chemotherapy¹³⁶. Treatment of the primary tumour has also shown a survival benefit in men with oligometastatic disease, and a few trials are currently

assessing the effect of metastasis-directed therapy for these men¹³⁷⁻¹⁴⁰. Considering these advances, more precise staging with PSMA PET/CT will likely become standard of practice in order to provide the best treatment available.

In registry-based research, analysis of different time periods may be hindered by changes in diagnostic modalities and definitions e.g. the grade inflation due to changes in ISUP classification. Similarly, management outcomes in men with M0 disease will be difficult to compare before and after the implementation of PSMA PET/CT, since a substantial number of men with M0 disease according to conventional imaging have signs of metastases on PSMA PET/CT¹³⁵.

Despite these difficulties, high quality registries such as PCBaSe are an invaluable source for population-based research and for monitoring adherence to evidence-based management. The data extraction protocols that are already in place can also be used to collect evidence for randomized interventions or treatments, saving cost and increasing generalizability. These study designs are referred to as registry-based randomized controlled trials and can be used to compare management options when multiple standards are already in use¹⁴¹.

Death of any cause is one of the most robust endpoints in cancer research, whereas death from a specific cause is subject to misclassification errors. The effects of both screening and treatment for prostate cancer in clinical trials is often based on prostate cancer death as an outcome, since effects on overall mortality may require an impractical number of study participants. In most population-based studies, the robustness of prostate cancer death as an outcome measure is heavily dependent on the quality of initial death certification. With autopsy rates in decline, the validity of death certification is predominantly reliable on review of medical notes. Physicians need to be aware of the importance of correctly identifying the cause of death and its implications for research. Interventions to improve death certification through education and training have proven effective and should be administered early in a physician's career¹⁴². Expert committee review increases the accuracy of death certification, however, the review process is time-consuming and resource-intensive. Recently, machine learning tools are evolving that can predict prostate cancer death from free-text summaries of medical notes, with accuracy similar to expert review¹⁴³. Further development of such tools can hopefully lead to prediction accuracy close to the gold standard i.e. death certification by autopsy.

The limitation of PSA testing for early diagnosis of prostate cancer has long been understood¹⁴⁴. In recent years, the diagnostic arena of prostate cancer has evolved rapidly with the development of mpMRI of the prostate, which is now a routine imaging procedure for men with moderately elevated PSA. Results have shown that compared with standard biopsy, the use of MRI targeted biopsy may half the risk of diagnosing low-risk prostate cancer,

without missing clinically significant tumours¹⁴⁵. This could be a turning point for future screening policies since the benefit of screening has in previous trials not clearly outweighed the risks of overdiagnosis^{25,26}.

In this thesis we have shown that prostate cancer survival and mortality is strongly affected by different biases, particularly for old men and men with low-risk prostate cancer. Efforts to decrease the detection of clinically insignificant tumours, along with education and awareness of death certification, and further development of prediction tools for the adjudication of death will increase the accuracy of mortality statistics for men with prostate cancer.

Swedish summary

Bakgrund

I början av 1900-talet var prostatacancer en ovanlig cancer men dödligheten var hög. Nu är prostatacancer den vanligaste canceren i Sverige, varje år diagnostiseras cirka 10 000 män med prostatacancer och cirka 2 500 män dör av denna cancer. I början av 1990-talet upptäcktes att prostata-specifikt antigen (PSA) kan användas för att detektera prostatacancer i tidigt skede. Det tillsammans med införandet av ultraljudsledd biopsi ledde till en kraftig ökning av fall av prostatacancer, framför allt lågrisk prostatacancer. Detta har gjort att prostatacancer vården har förändrats dramatiskt under de senaste 25 åren. Samtidigt har prostatacancer dödligheten minskat något, bland annat på grund av mer behandling med prostatektomi, strålbehandling och hormoner.

I denna avhandling undersöktes hur dödligheten har ändrats i Sverige och vi använde flera metoder för att undersöka detta. Avhandlingen bygger på data från Prostate Cancer data Base Sweden (PCBaSe), en forskningsdatabas baserat på information i Nationella prostatacancerregistret (NPCR) som har länkats till andra nationella hälsovårdsregister och demografiska databaser, inklusive Patientregistret, Läkemedelsregistret och Dödsorsaksregistret. NPCR innehåller 98% av alla män med prostatacancer som är registrerade i Cancerregistret.

Delarbete I

I delarbete I undersökte vi om ökningen av primär radikal behandling d.v.s. strålbehandling eller radikal prostatektomi, har minskat dödligheten bland alla män med lokalt avancerad prostatacancer mellan 2000 och 2016 i Sverige. 20 350 män med lokalt avancerat prostatacancer identifierades i PCBaSe.

Andelen män som fick primär radikal behandling tredubblades bland män yngre än 80 år, från 22% till 64%. Andelen strålbehandlade män ökade från 18% till 48% och andelen män som genomgick prostatektomi ökades från 4% till 15%. Samtidigt minskade den kumulativa incidensen av prostatacancerdöd bland män yngre än 80 år från 17% till 10%. Mindre än en procent

(48/6159) av män över 80 år fick radikal behandling. Dödligheten i prostatacancer var oförändrad bland män över 85 år.

Efter justering för störfaktorerna ålder, PSA, T-stadium, M-stadium, samsjuklighet, civilstånd och utbildningsnivå förblev risken för prostatacancer död lägre under den sista studieperioden jämfört med den första, hasardkvot 0.65 (95% konfidensintervall 0.56-0.76). Efter justering för radikal behandling försvann skillnaden i prostatacancerdödlighet mellan perioderna.

Våra resultat antyder att det mesta av minskningen i dödlighet av prostatacancer bland män med lokalt avancerad prostatacancer de senaste två decennierna förklaras av ökad användning av radikal behandling, speciellt strålbehandling.

Delarbete II

I delarbete II jämfördes relativ och cancerspecifik överlevnad bland 168 793 män yngre än 90 år som diagnostiserats med prostatacancer och registrerats i NPCR mellan 2000 och 2016.

Fem år efter diagnos var den relativa överlevnaden högre än den cancerspecifika överlevnaden i hela kohorten, 90% vs. 87%. Skillnaden mellan relativ och cancerspecifik femårsöverlevnad var särskilt stor bland män 80–89 år med lågrisk prostatacancer, 116% vs. 96%, och bland män med mellanrisk prostatacancer, 112% vs. 92%. Däremot var överlevnaden bland män med regionala eller fjärrmetastaser lika lång beräknad med bägge metoderna.

Efter justering för samsjuklighet, civilstånd och utbildningsgrad, minskade den relativa femårsöverlevnaden bland män 80–89 år med lågrisk prostatacancer från 116% till 106%.

Våra resultat visar att både relativ och cancerspecifik överlevnad har brister som mått på överlevnad bland äldre män med låg eller mellanrisk prostatacancer eftersom dessa män i snitt är friskare än bakgrundspopulationen.

Delarbete III

I delarbete III eftergranskades evidens för prostatacancerdöd bland 495 män som dog av prostatacancer enligt Dödsorsaksregistret mellan 2011 och 2018 i Sverige. Sköterskor på 20 sjukhus i Sverige studerade alla tillgängliga journalhandlingar för att söka evidens för progredierande sjukdom, till exempel stigande PSA, bildundersökningar som visade metastaser etc.

Vi graderade den totala evidensen för prostatacancerdöd med hjälp av poängsystem: 0 poäng – ingen evidens, 1 poäng – måttlig evidens, 2 poäng – stark evidens, 3-9 poäng – mycket stark evidens.

Män över 80 år hade oftare ingen eller måttligt med evidens för prostatacancerdöd jämfört med yngre män, 29% vs. 14%. Graden av evidens var

lika hög oavsett riskkategori vid diagnos bland dessa män. Däremot var andelen yngre män utan eller med måttlig evidens för prostatacancerdöd högre hos män med lågrisk än dem med spridd cancer, 21% för lågrisk, 8% för högrisk och 0% för spridd prostatacancer. Vi beräknade att 13% av alla män i NPCR med prostatacancer som dödsorsak i Dödsorsaksregistret hade ingen eller måttlig evidens för prostatacancerdöd. Denna andel var dubbelt så hög bland män över 80 och bland män med lågrisk prostatacancer.

Resultaten visar att risk för felklassificering av prostatacancer som dödsorsak är högre bland äldre män och män med lågrisk prostatacancer eftersom dödsorsaksbestämningen för dessa män var baserad på en låg grad av evidens.

Delarbete IV

I delarbete IV undersöktes hur diagnostisk aktivitet och förväntad livslängd påverkar livstidsrisken för prostatacancerdiagnos. Vi simulerade livstidsrisk för prostatacancer bland 2 000 000 män i åldern 40 till 100 år. Vi undersökte tre nivåer av diagnostisk aktivitet och tre olika nivåer av förväntad livslängd.

Män som var exponerade för hög diagnostisk aktivitet hade fem gånger högre livstidsrisk för låg eller mellanrisk prostatacancer men halverad risk för högriskcancer jämfört med män exponerade för låg aktivitet. Män med lång förväntad livslängd hade något högre livstidsrisk för prostatacancer jämfört med män med kort förväntad överlevnad.

Våra resultat visar att livstidsrisken för prostatacancer är starkt kopplad till diagnostisk aktivitet och till mindre del till förväntad livslängd.

Slutsatser

Vi fann att dödligheten bland män med lokalt avancerad prostatacancer minskat de senaste decennierna, troligen till följd av ökad användning av framförallt strålterapi. Äldre män som diagnostiserats med prostatacancer, framförallt lågriskcancer är friskare än män i bakgrundsbefolkningen. Därför är valet av metod för analys av dödlighet och överlevnad viktig och resultaten ska bedömas med försiktighet eftersom det finns en felklassifikation av dödsorsak bland en stor andel av dessa män.

Acknowledgements

Pär Stattin – Professor of Urology and my main supervisor. For believing in me and inviting me to move from Iceland to Uppsala in pursuit of a career in research and residency in Urology at Akademiska hospital. I could not have asked for a better guidance during my time as a PhD student. Your feedback has always been prompt, sharp and reconstructive; from “bra, men kan bli bättre” to “immer besser”.

Hans Garmo – Co-supervisor and senior statistician. For always be willing to meet and discuss ideas when my mind was “statistically” at unease. A more clinically skilled statistician is hard to find.

Marcus Westerberg – Statistician. For all your statistical assistance and feedback, and for coaching me in the R software during my first year. Without a doubt a rising star in the world of statistics.

Paul Dickman – Professor of Biostatistics. For all your advice and assistance on net survival. Thank you for inviting me to visit Karolinska and meet all your talented colleagues.

Eva Johansson – Head of the department of Urology. For giving me the flexibility to combine research with clinical work and for enabling me to evolve and gain confidence in the operating wound.

Tómas Guðbjartsson – Professor of Cardiothoracic Surgery. For motivating me to pursue a surgical career and giving me wings to research.

Inrapportörer NPCR – For your hard work collecting evidence of prostate cancer progression. Without you paper III would not have been possible.

To all my **fellow colleagues** at the Department of Urology.

To my boat crew, **Rafaele and Birkir**, for recharging my batteries.

To my brother, **Leifur**, for his help with the cover photo and design advice.

To my love, **Kristell**, for endless support through the whole journey.

References

1. ECIS - European Cancer Information System. <https://ecis.jrc.ec.europa.eu>. Accessed 03.24, 2022.
2. Gandaglia G, Abdollah F, Schiffmann J, et al. Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. *The Prostate*. 2014;74(2):210-216.
3. Ferlay J EM, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). <https://gco.iarc.fr/today>. Accessed 05.04.2021.
4. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *International journal of cancer*. 2015;137(7):1749-1757.
5. National Board of Health and Welfare in Sweden. Cancer Statistics. https://sdb.socialstyrelsen.se/if_can/. Accessed 24.03, 2022.
6. The National Prostate Cancer Register of Sweden. Data register for diagnosis and treatment of prostate cancer. www.npcr.se.
7. Cancer Statistics for the Nordic Countries. <http://www-dep.iarc.fr/NORDCAN.htm>.
8. Kheirandish P, Chingewundoh F. Ethnic differences in prostate cancer. *British journal of cancer*. 2011;105(4):481-485.
9. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. *J Natl Cancer Inst*. 2005;97(19):1407-1427.
10. Mucci LA, Hjelmberg JB, Harris JR, et al. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA*. 2016;315(1):68-76.
11. Kiciński M, Vangronsveld J, Nawrot TS. An Epidemiological Reappraisal of the Familial Aggregation of Prostate Cancer: A Meta-Analysis. *PloS one*. 2011;6(10):e27130.
12. Bratt O, Drevin L, Akre O, Garmo H, Stattin P. Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study. *JNCI: Journal of the National Cancer Institute*. 2016;108(10).
13. Lee J, Demissie K, Lu SE, Rhoads GG. Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea. *Cancer control : journal of the Moffitt Cancer Center*. 2007;14(1):78-85.
14. Mandair D, Rossi R, Pericleous M, Whyand T, Caplin M. Prostate cancer and the influence of dietary factors and supplements: A systematic review. *Nutrition & metabolism*. 2014;11:30.

15. Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2003;21(2):383-391.
16. Holmström B, Johansson M, Bergh A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: longitudinal study. *BMJ (Clinical research ed)*. 2009;339:b3537.
17. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. *Prostate cancer and prostatic diseases*. 2018;21(1):57-63.
18. Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. *Journal of general internal medicine*. 2000;15(10):739-748.
19. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *The Journal of urology*. 1989;142(1):71-74; discussion 74-75.
20. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic Review of Complications of Prostate Biopsy. *European urology*. 2013;64(6):876-892.
21. Lundström KJ, Drevin L, Carlsson S, et al. Nationwide population based study of infections after transrectal ultrasound guided prostate biopsy. *The Journal of urology*. 2014;192(4):1116-1122.
22. Distler FA, Radtke JP, Bonekamp D, et al. The Value of PSA Density in Combination with PI-RADS™ for the Accuracy of Prostate Cancer Prediction. *The Journal of urology*. 2017;198(3):575-582.
23. Washino S, Okochi T, Saito K, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naïve patients. *BJU international*. 2017;119(2):225-233.
24. Falagario UG, Jambor I, Lantz A, et al. Combined Use of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic Resonance Imaging Outcome Database (PROMOD). *European urology oncology*. 2021;4(6):971-979.
25. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet (London, England)*. 2014;384(9959):2027-2035.
26. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360(13):1310-1319.
27. Stark JR, Mucci L, Rothman KJ, Adami HO. Screening for prostate cancer remains controversial. *BMJ (Clinical research ed)*. 2009;339:b3601.
28. UICC (Union internationale Contre le Cancer). TNM Classification of Malignant Tumours., 8th ed. Geneva (Switzerland): International Union Against Cancer, 2017. 2017.
29. Gleason DF. Classification of prostatic carcinomas. *Cancer chemotherapy reports*. 1966;50(3):125-128.
30. Humphrey PA. Gleason grading and prognostic factors in carcinoma of the prostate. *Modern Pathology*. 2004;17(3):292-306.

31. Epstein JI, Amin MB, Reuter VE, Humphrey PA. Contemporary Gleason Grading of Prostatic Carcinoma: An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *The American journal of surgical pathology*. 2017;41(4):e1-e7.
32. Kryvenko ON, Epstein JI. Changes in prostate cancer grading: Including a new patient-centric grading system. *The Prostate*. 2016;76(5):427-433.
33. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *Jama*. 1998;280(11):975-980.
34. Fosså SD, Wiklund F, Klepp O, et al. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. *European urology*. 2016;70(4):684-691.
35. Egevad L, Delahunt B, Bostwick DG, et al. Prostate cancer grading, time to go back to the future. *BJU international*. 2021;127(2):165-168.
36. Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2010;8(2):162-200.
37. Van Hemelrijck M, Wigertz A, Sandin F, et al. Cohort Profile: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. *International Journal of Epidemiology*. 2012;42(4):956-967.
38. Abdollah F, Suardi N, Gallina A, et al. Extended pelvic lymph node dissection in prostate cancer: a 20-year audit in a single center. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2013;24(6):1459-1466.
39. Rider JR, Sandin F, Andren O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *European urology*. 2013;63(1):88-96.
40. Akre O, Garmo H, Adolfsson J, Lambe M, Bratt O, Stattin P. Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBaSe Sweden. *European urology*. 2011;60(3):554-563.
41. Fellows GJ, Clark PB, Beynon LL, et al. Treatment of advanced localised prostatic cancer by orchiectomy, radiotherapy, or combined treatment. A Medical Research Council Study. Urological Cancer Working Party--Subgroup on Prostatic Cancer. *British journal of urology*. 1992;70(3):304-309.
42. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *International journal of radiation oncology, biology, physics*. 2005;61(5):1285-1290.
43. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360(24):2516-2527.

44. Mason MD, Parulekar WR, Sydes MR, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(19):2143-2150.
45. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet (London, England)*. 2009;373(9660):301-308.
46. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *European urology*. 2017;71(4):618-629.
47. Nationella riktlinjer för prostatacancer. www.socialstyrelsen.se.
48. Ploussard G, Agamy MA, Alenda O, et al. Impact of positive surgical margins on prostate-specific antigen failure after radical prostatectomy in adjuvant treatment-naïve patients. 2011;107(11):1748-1754.
49. Meeks JJ, Eastham JA. Radical prostatectomy: Positive surgical margins matter. *Urologic Oncology: Seminars and Original Investigations*. 2013;31(7):974-979.
50. Fahmy O, Khairul-Asri MG, Hadi S, Gakis G, Stenzl A. The Role of Radical Prostatectomy and Radiotherapy in Treatment of Locally Advanced Prostate Cancer: A Systematic Review and Meta-Analysis. *Urologia internationalis*. 2017;99(3):249-256.
51. Wang Z, Ni Y, Chen J, et al. The efficacy and safety of radical prostatectomy and radiotherapy in high-risk prostate cancer: a systematic review and meta-analysis. *World J Surg Oncol*. 2020;18(1):42-42.
52. Moris L, Cumberbatch MG, Van den Broeck T, et al. Benefits and Risks of Primary Treatments for High-risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review. *European urology*. 2020;77(5):614-627.
53. Robinson D, Garmo H, Lissbrant IF, et al. Prostate Cancer Death After Radiotherapy or Radical Prostatectomy: A Nationwide Population-based Observational Study. *European urology*. 2018;73(4):502-511.
54. Stranne J, Brasso K, Brennhovd B, et al. SPCG-15: a prospective randomized study comparing primary radical prostatectomy and primary radiotherapy plus androgen deprivation therapy for locally advanced prostate cancer. *Scandinavian journal of urology*. 2018;1-8.
55. Hager B, Kraywinkel K, Keck B, et al. Increasing use of radical prostatectomy for locally advanced prostate cancer in the USA and Germany: a comparative population-based study. *Prostate cancer and prostatic diseases*. 2017;20(1):61-66.
56. Yearly Report on Prostate Cancer (in swedish). National Prostate Cancer Registry of Sweden. 2018; http://nprc.se/wp-content/uploads/2019/09/20190905_nprc_nationell_rapport_2018.pdf. Accessed 01.10., 2020.
57. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*. 1958;53(282):457-481.

58. Mariotto AB, Noone AM, Howlader N, et al. Cancer survival: an overview of measures, uses, and interpretation. *Journal of the National Cancer Institute Monographs*. 2014;2014(49):145-186.
59. DICKMAN PW, ADAMI H-O. Interpreting trends in cancer patient survival. 2006;260(2):103-117.
60. Ederer F HH. Instructions to IBM 650 Programmers in Processing Survival Computations. Methodological Note No. 10. *End Results Evaluation Section Bethesda (MD): National Cancer Institute*. 1959.
61. Forjaz de Lacerda G, Howlader N, Mariotto AB. Differences in Cancer Survival with Relative versus Cause-Specific Approaches: An Update Using More Accurate Life Tables. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2019;28(9):1544-1551.
62. Skyrud KD, Bray F, Møller B. A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis. 2014;135(1):196-203.
63. Makkar N, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. A comparison of relative survival and cause-specific survival methods to measure net survival in cancer populations. *Cancer medicine*. 2018;7(9):4773-4780.
64. Fall K, Stromberg F, Rosell J, Andren O, Varenhorst E. Reliability of death certificates in prostate cancer patients. *Scandinavian journal of urology and nephrology*. 2008;42(4):352-357.
65. Löffeler S, Halland A, Weedon-Fekjær H, Nikitenko A, Ellingsen CL, Haug ES. High Norwegian prostate cancer mortality: evidence of over-reporting. *Scandinavian journal of urology*. 2018;52(2):122-128.
66. Bright CJ, Brentnall AR, Wooldrage K, Myles J, Sasieni P, Duffy SW. Errors in determination of net survival: cause-specific and relative survival settings. *British journal of cancer*. 2020;122(7):1094-1101.
67. Withrow DR, Pole JD, Nishri ED, Tjepkema M, Marrett LD. Choice of relative or cause-specific approach to cancer survival analysis impacts estimates differentially by cancer type, population, and application: evidence from a Canadian population-based cohort study. *Population health metrics*. 2017;15(1):24.
68. Howlader N, Ries L, Mariotto A, Reichman M, Ruhl J, Cronin K. Improved Estimates of Cancer-Specific Survival Rates From Population-Based Data. *Journal of the National Cancer Institute*. 2010;102:1584-1598.
69. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *International Journal of Epidemiology*. 2010;39(2):598-610.
70. Eloranta S, Adolffson J, Lambert PC, et al. How can we make cancer survival statistics more useful for patients and clinicians: an illustration using localized prostate cancer in Sweden. *Cancer Causes Control*. 2013;24(3):505-515.
71. World Health Organization. Global Health Observatory. Geneva: World Health Organization. who.int/gho/database/en/. Accessed January, 2020.
72. National Board of Health and Welfare. Cause of Death Statistics. https://sdb.socialstyrelsen.se/if_dor/val.aspx. Accessed 24.03, 2022.

73. Bechis SK, Carroll PR, Cooperberg MR. Impact of Age at Diagnosis on Prostate Cancer Treatment and Survival. *Journal of Clinical Oncology*. 2010;29(2):235-241.
74. Bratt O, Folkvaljon Y, Hjalml Eriksson M, et al. Undertreatment of Men in Their Seventies with High-risk Nonmetastatic Prostate Cancer. *European urology*. 2015;68(1):53-58.
75. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *European journal of epidemiology*. 2017;32(9):765-773.
76. Organisation WH. *International statistical classification of diseases and related health problems—10th revision*. Geneva: World Health Organisation; 2016.
77. Walter SD, de Koning HJ, Hugosson J, et al. Impact of cause of death adjudication on the results of the European prostate cancer screening trial. *British journal of cancer*. 2017;116(1):141-148.
78. Godtman R, Holmberg E, Stranne J, Hugosson J. High accuracy of Swedish death certificates in men participating in screening for prostate cancer: a comparative study of official death certificates with a cause of death committee using a standardized algorithm. *Scandinavian journal of urology and nephrology*. 2011;45(4):226-232.
79. Mäkinen T, Karhunen P, Aro J, Lahtela J, Määttänen L, Auvinen A. Assessment of causes of death in a prostate cancer screening trial. *International journal of cancer*. 2008;122(2):413-417.
80. Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *The Journal of urology*. 2000;163(2):519-523.
81. Penson DF, Albertsen PC, Nelson PS, Barry M, Stanford JL. Determining Cause of Death in Prostate Cancer: Are Death Certificates Valid? *JNCI: Journal of the National Cancer Institute*. 2001;93(23):1822-1823.
82. Baker SG, Kramer BS, Prorok PC. Statistical issues in randomized trials of cancer screening. *BMC Med Res Methodol*. 2002;2:11.
83. Cashman RE, Gerhardt PR, Goldberg ID, Handy VH, Levin ML. The probability of developing cancer. *J Natl Cancer Inst*. 1956;17(2):155-173.
84. Day NE MC, Waterhouse J, Mack T, Powell J, Whelan S. Cumulative rates and cumulative risk. In *Cancer Incidence in Five Continents vol. V. International Agency for Research on Cancer*. 1987:787-789.
85. (NORDCAN) CsftNc. <https://nordcan.iarc.fr/>. Accessed 22.12, 2021.
86. Taitt HE. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. *American journal of men's health*. 2018;12(6):1807-1823.
87. Cancer Research UK. Office for National Statistics (ONS) 2016-based Life expectancies and population projections. 2016; <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/risk-factors#ref1>. Accessed 27. September, 2021.
88. National Cancer Institute. SEER Cancer Stat Facts: Prostate Cancer. <https://seer.cancer.gov/statfacts/html/prost.html>. Accessed 27. September, 2021.

89. Fay MP, Pfeiffer R, Cronin KA, Le C, Feuer EJ. Age-conditional probabilities of developing cancer. *Statistics in medicine*. 2003;22(11):1837-1848.
90. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *British journal of cancer*. 2016;115(9):1147-1155.
91. Pathirana T, Hayen A, Doust J, Glasziou P, Bell K. Lifetime risk of prostate cancer overdiagnosis in Australia: quantifying the risk of overdiagnosis associated with prostate cancer screening in Australia using a novel lifetime risk approach. *BMJ open*. 2019;9(3):e022457.
92. Lloyd T, Hounscome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. *BMC medicine*. 2015;13:171.
93. Miller BA, Scoppa SM, Feuer EJ. Racial/ethnic patterns in lifetime and age-conditional risk estimates for selected cancers. *Cancer*. 2006;106(3):670-682.
94. Westerberg M, Larsson R, Holmberg L, Stattin P, Garmo H. Simulation model of disease incidence driven by diagnostic activity. *Statistics in medicine*. 2021;40(5):1172-1188.
95. Bergengren O, Westerberg M, Holmberg L, Stattin P, Bill-Axelsson A, Garmo H. Variation in Prostate-Specific Antigen Testing Rates and Prostate Cancer Treatments and Outcomes in a National 20-Year Cohort. *JAMA network open*. 2021;4(5):e219444.
96. Tomic K, Berglund A, Robinson D, et al. Capture rate and representativity of The National Prostate Cancer Register of Sweden. *Acta oncologica (Stockholm, Sweden)*. 2015;54(2):158-163.
97. Van Hemelrijck M, Garmo H, Wigertz A, Nilsson P, Stattin P. Cohort Profile Update: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base--a refined prostate cancer trajectory. *International journal of epidemiology*. 2016;45(1):73-82.
98. Van Hemelrijck M, Wigertz A, Sandin F, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. *Int J Epidemiol*. 2013;42(4):956-967.
99. Stattin P, Sandin F, Sandbäck T, et al. Dashboard report on performance on select quality indicators to cancer care providers. *Scandinavian journal of urology*. 2016;50(1):21-28.
100. Stattin P, Sandin F, Loeb S, Robinson D, Lissbrant IF, Lambe M. Public online reporting from a nationwide population-based clinical prostate cancer register. *BJU international*. 2018;122(1):8-10.
101. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology*. 2004;57(12):1288-1294.
102. The Human Mortality Database. www.mortality.org. Accessed 01.08.2019.
103. Brenner H, Rachet B. Hybrid analysis for up-to-date long-term survival rates in cancer registries with delayed recording of incident cases. *European journal of cancer (Oxford, England : 1990)*. 2004;40(16):2494-2501.
104. Perme MP, Stare J, Esteve J. On estimation in relative survival. *Biometrics*. 2012;68(1):113-120.

105. R Gedeberg HG, D Robinson, Pär Stattin. Prescription-based prediction of baseline mortality risk among older men in Sweden. *Manuscript*. 2020.
106. Cochran WG. *Sampling Techniques, 3rd edition*. Wiley New York, NY, USA 1977.
107. Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *The Lancet Oncology*. 2015;16(16):1667-1676.
108. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. *JAMA*. 2016;316(17):1818-1819.
109. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
110. Westerberg M, Franck Lissbrant I, Damber JE, Robinson D, Garmo H, Stattin P. Temporal changes in survival in men with de novo metastatic prostate cancer: nationwide population-based study. *Acta oncologica (Stockholm, Sweden)*. 2020;59(1):106-111.
111. Westerberg M, Franck Lissbrant I, Damber JE, Robinson D, Garmo H, Stattin P. Temporal changes in survival in men with de novo metastatic prostate cancer: nationwide population-based study. *Acta Oncologica*. 2020;59(1):106-111.
112. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *The Lancet Oncology*. 2007;8(6):475-487.
113. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MFH, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiotherapy and Oncology*. 2014;110(1):104-109.
114. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *The Lancet*. 2019;394(10196):385-395.
115. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The Lancet Oncology*. 2016;17(8):1047-1060.
116. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *International journal of radiation oncology, biology, physics*. 2019;104(4):778-789.
117. Kishan AU, Cook RR, Ciezki JP, et al. Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer. *Jama*. 2018;319(9):896-905.
118. Wedde TB, Småstuen MC, Brabrand S, et al. Ten-year survival after High-Dose-Rate Brachytherapy combined with External Beam Radiation Therapy in high-risk prostate cancer: A comparison with the Norwegian SPCG-7 cohort. *Radiotherapy and Oncology*. 2019;132:211-217.

119. Mottet N, Briers E, Bolla M, Bourke L, Cornford P, De Santis M, Henry A, Joniau S, Lam T, Mason M.D., Van den Poel H, Van den Kwast T.H., Rouvière O, Wiegel T.; members of the EAU – ESTRO – ESUR – SIOG Prostate Cancer Guidelines Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. <https://uroweb.org/guideline/prostate-cancer/> Accessed 06.03.2022, 2021.
120. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(35):3939-3947.
121. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *The Lancet Oncology*. 2020;21(10):1331-1340.
122. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet (London, England)*. 2020;396(10260):1413-1421.
123. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *The Lancet Oncology*. 2020;21(10):1341-1352.
124. Stattin P, Sandin F, Thomsen FB, et al. Association of Radical Local Treatment with Mortality in Men with Very High-risk Prostate Cancer: A Semiecologic, Nationwide, Population-based Study. *European urology*. 2017;72(1):125-134.
125. Hoffman RM, Stone SN, Espey D, Potosky AL. Differences between men with screening-detected versus clinically diagnosed prostate cancers in the USA. *BMC cancer*. 2005;5(1):27.
126. Røder MA, Brasso K, Berg KD, et al. Patients undergoing radical prostatectomy have a better survival than the background population. *Danish medical journal*. 2013;60(4):A4612.
127. Stattin P, Holmberg E, Johansson J-E, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *Journal of the National Cancer Institute*. 2010;102(13):950-958.
128. Rosendahl A, Mjörnheim B, Eriksson LC. Autopsies and quality of cause of death diagnoses. *SAGE open medicine*. 2021;9:20503121211037169.
129. Rosendahl A, Mjörnheim B, Takman C, Eriksson LC. The clinical value of autopsies at a university hospital in Sweden. *Nordic Journal of Nursing Research*. 2016;37(3):119-126.
130. Hernes E, Johansson L, Fosså S, Harvei S, Gjertsen F, Glatte E. *Prostate cancer (PC) mortality rates: Manual versus ACME (Automated Classification of Medical Entities) coding*. Vol 222004.
131. National Board of Health and Welfare. Life expectancy 1751–2020. <https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/pong/tables-and-graphs/yearly-statistics--the-whole-country/life-expectancy/>. Accessed 26.09.2021.
132. Sweden TNPCRo. <https://statistik.incanet.se/npcr/>. Accessed 14.03, 2022.

133. 2018–2070. SSTfpoS. www.scb.se. Accessed 17.03, 2022.
134. Bratt O, Folkvaljon Y, Hjälm Eriksson M, et al. Undertreatment of Men in Their Seventies with High-risk Nonmetastatic Prostate Cancer. *European urology*. 2015;68(1):53-58.
135. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *The Lancet*. 2020;395(10231):1208-1216.
136. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. 2022;386(12):1132-1142.
137. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet (London, England)*. 2018;392(10162):2353-2366.
138. Boevé LMS, Hulshof M, Vis AN, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. *European urology*. 2019;75(3):410-418.
139. Thureau S, Marchesi V, Vieillard MH, et al. Efficacy of extracranial stereotactic body radiation therapy (SBRT) added to standard treatment in patients with solid tumors (breast, prostate and non-small cell lung cancer) with up to 3 bone-only metastases: study protocol for a randomised phase III trial (STEREO-OS). *BMC cancer*. 2021;21(1):117.
140. De Bruycker A, Spiessens A, Dirix P, et al. PEACE V - Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. *BMC cancer*. 2020;20(1):406.
141. Karanatsios B, Prang K-H, Verbunt E, Yeung JM, Kelaher M, Gibbs P. Defining key design elements of registry-based randomised controlled trials: a scoping review. *Trials*. 2020;21(1):552.
142. Gamage USH, Mahesh PKB, Schnall J, et al. Effectiveness of training interventions to improve quality of medical certification of cause of death: systematic review and meta-analysis. *BMC medicine*. 2020;18(1):384.
143. McWilliams C, Walsh EI, Huxor A, Turner EL, Santos-Rodriguez R. Predicting cause of death from free-text health summaries: development of an interpretable machine learning tool. 2021:2021.2007.2015.21260082.
144. Slatkoff S, Gamboa S, Zolotor AJ, Mounsey AL, Jones K. PURLs: PSA testing: when it's useful, when it's not. *The Journal of family practice*. 2011;60(6):357-360.
145. Eklund M, Jäderling F, Discacciati A, et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. 2021;385(10):908-920.

Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 1836*

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-471670



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2022