Prostate cancer in three Nordic countries

- The impact of diagnostic and therapeutic strategies on incidence, trends in clinical presentation and management

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Blöðruhálskirtilskrabbamein hjá þremur norrænum þjóðum

- Áhrif greiningar og meðferðarstefnu á nýgengi, þróun klínískra þátta og meðferð

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ÁGRIP

Blöðruhálskirtilskrabbamein er í dag algengasta krabbamein meðal karlmanna bæði á Íslandi og í Danmörku. Í byrjun 10. áratugar síðustu aldar kom fram á sjónarsviðið svokallað PSA-blóðpróf. PSA er stytting á heitinu *prostate specific antigen* en það er sameind sem blöðruhálskirtilinn framleiðir. Hækkað blóðgildi PSA getur gefið til kynna að blöðruhálskrabbamein sé til staðar. PSA er hins vegar ekki sértækt fyrir krabbamein og getur einnig mælst hækkað í öðrum algengum kvillum í blöðruhálskirtlinum s.s. bólgu og góðkynja stækkun. Fljótlega eftir innleiðingu PSA-blóðprófsins kom í ljós að norrænir heilbrigðisstarfsmenn notuðu prófið mismikið til að greina blöðruhálskirtilskrabbamein á frumstigi. Öll Norðurlöndin búa yfir lýðgrundaðri krabbameinskrá. Faraldsfræðilegar rannsóknir, byggðar á gögnum úr þessum krabbameinsskrám, hafa sýnt fram á verulegan mun á nýgengi og lifun meðal norrænna sjúklinga með blöðruhálskirtilskrabbamein. Í Danmörku reyndist nýgengi blöðruhálskirtils–krabbameins vera lægra, auk þess sem þessi sjúklingahópur lifði mun skemur. Aftur á móti hefur dánartíðni blöðruhálskirtilskrabbameinssjúklinga meðal Norðurlandaþjóðanna haldist svipuð frá miðjum 9. áratug síðustu aldar.

Þessi doktorsritgerð felur í sér rannsókn sem skoðar sérstaklega þá sjúklinga sem greindust með blöðruhálskirtilskrabbamein kringum árið 1997 en þá var Danmörk enn sér á báti varðandi nýgengi og lifun. Á rannsóknartímabilinu var blöðruhálskirtilskrabbamein þegar orðið algengasta krabbamein meðal íslenskra karlmanna en var í þriðja sæti meðal krabbameina hjá dönskum karlmönnum. Faraldsfræðilegar rannsóknir byggðar á gögnum frá krabbameinsskrám hafa ekki innihaldið klínískar upplýsingar og með því að afla þeirra á kerfisbundinn hátt veitir ritgerðin frekari skýringar á þessum mismun. Ennfremur er í ritgerðinni framkvæmt gæðamat á þeim klínísku upplýsingum sem höfðu verið tilkynntar til dönsku krabbameinskrárinnar kringum 1997 varðandi danska sjúklinga með blöðruhálskirtilskrabbamein.

Helstu niðurstöður sem komu fram í rannsókninni eru eftirfarandi:

Hlutfallsleg lifun sjúklingaþýða rannsóknarinnar var sambærileg við fyrri rannsóknir sem byggja á almennum gögnum úr krabbameinsskrám. Munurinn á hlutfalli sjúklinga með fjarmeinvörp við greiningu úskýrði að mestu leyti muninn á hlutfallslegri lifun milli landanna. Þegar leiðrétt var fyrir öðrum þáttum, s.s.

útbreiðslu sjúkdómsins, æxlisstigi (T-stigi) og PSA gildi, minnkaði eða hvarf munirinn alveg.

Flestir þeirra sjúklinga sem greindust með staðbundið blöðruhálskirtils–krabbamein í Danmörku og á Íslandi höfðu upphaflega leitað læknis vegna neðri þvagvegaeinkenna. Í Danmörku var greiningin að langmestu leyti staðfest með heflun úr blöðruhálskirtlinum (TURP) en á Íslandi með grófnálarsýni úr blöðruhálskirtlinum. Íslensku sjúklingarnir voru yngri og fleiri greindust á fyrstu stigum sjúkdómsins, auk þess sem uppvinnsla þeirra var ítarlegri. Læknanleg meðferð og hormónameðferð var oftar veitt á Íslandi.

Svipuð þróun og hafði átt sér stað á Íslandi sást um fimm árum síðar í Danmörku, þ.e. hækkun á nýgengi blöðruhálskirtilskrabbameins, breytt aldursdreifing og hækkun á hlutfalli staðbundins krabbameins.

Upplýsingar um stigun og meðferð sem bárust dönsku krabbameinsskránni voru ónákvæmar. Þetta kann að rýra gæði þeirra rannsókna sem byggjast eingöngu á gögnum frá krabbameinsskrám. Greiningardagur, sem tilkynntur var til dönsku krabbameinskrárinnar og sá sem skráður var úr sjúkragögnum, var sá hinn sami í 70% tilvika. Hins vegar höfðu um 95% tilfella minni en þriggja mánaða mun á tímasetningu greiningardags. Leiðrétting fyrir greiningardegi hafði engin áhrif á lifun.

Loks sýnir ritgerðin fram á að lifun danskra manna sem greindust með blöðruhálskirtilskrabbamein hefur aukist marktækt frá árinu 1997 fram til tímabilsins 2007-2013. Ástæður fyrir því geta að miklu leyti verið vegna greiningarforskotsbjögunar (lead-time bias) en einnig vægi nýrra lífslengjandi meðferða.

ABSTRACT

Each Nordic country has a population-based cancer registry dating back to the 1940s or 1950s, and the notification of a cancer diagnosis is mandatory. With the advent of prostate-specific antigen level (PSA) testing in the early 1990s, Nordic countries differed in their approach towards early detection of prostate cancer (PC) and treatment. This was reflected in differences in PC incidence in the nineties with higher incidence in all the Nordic countries except in Denmark. Register-based studies showed survival differences among PC patients, with poorer outcomes in Denmark.

The aim of this project was to shed a light on this difference by gathering clinical data that could facilitate the interpretation of incidence and mortality trends, elucidate reasons for differences in survival, and evaluate the quality of register-based data. In Paper I, the survival of a population-based Icelandic cohort and counterparts for the Danish and Swedish populations are analysed by comparing various clinical parameters. In Paper II, only Danish and Icelandic cases with localised disease are compared. Paper III studies the incidence and mortality trends in Denmark based on register data, and Paper IV comprises a quality assessment of register data. Paper V compares the survival of patients with metastatic PC in two different time periods in Denmark.

Relative survival in the study cohorts is comparable to previous population-based studies. Significant differences in excess mortality rates are found across countries, which diminish or disappear after adjustment for patient characteristics, e.g. metastatic status, clinical tumour stage (T stage) and PSA level. A difference in the proportion of patients with metastatic disease is the main explanation of the differences in survival rates among countries, while the incidence rates of metastatic cancer are similar.

Among patients with localised PC in Denmark and Iceland, lower urinary tract symptoms (LUTS) were the predominant clinical presentation. Diagnosis was commonly confirmed by transurethral resection of the prostate (TURP) in Denmark, whereas in Iceland with Tru-cut biopsies. The Icelandic patients were younger, and a fivefold higher proportion of them were diagnosed with stage T1c. A higher proportion underwent bone imaging, had a normal PSA value and tumours of low Gleason grade. Treatment with curative intent and endocrine treatment were more common in Iceland. By stratifying according to M-stage, patients without metastatic disease had comparable outcomes during the first 4 years of follow-up; thereafter, survival of Danish patients was significantly poorer. A significant difference in survival of patients with unknown metastatic status was apparent during the entire follow-up period.

The changes in incidence rates in the 3 Nordic countries resemble those observed in Europe and the USA, reflecting first a rise in the number of TURP

procedures, but later an exponential rise in the use of PSA testing. A conservative approach towards early case finding in Denmark in the early 1990s contributed to the vast differences observed in incidence and survival. Radical prostatectomy became a routine procedure in Iceland around 1990 and was implemented in Denmark around 1995. The introduction of this radical treatment option along with an increase in public awareness of PC resulted in a sharp rise in PC incidence in both countries. Throughout the period studied, mortality rates have been similar in all 3 Nordic countries. Paper III shows that changes in age distribution and clinical stage in Denmark, especially among younger patients, indicated a shift towards a more active diagnostic policy after 1995. Danish Cancer Register (DCR) information on stage and treatment was found to be inaccurate and can reduce the quality of register-based studies. Date of diagnosis between the DCR and hospital papers matched in 70% of cases, though in 95% of cases, the difference was less than 3 months. Correction of dates of diagnosis had no impact on survival.

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“When we are no longer able to change a situation -
we are challenged to change ourselves”.

Victor Emil Frankl (1905-1997)

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LIST OF ABBREVIATIONS

ADT	Androgen-deprivation therapy
BPH	Benign prostate hyperplasia
CCI	Charlson comorbidity index
CI	Confidence interval
CRG	National Cancer Registers
DCR	Danish Cancer Registry
DRE	Digital rectal exploration
EPIC	European Prospective Investigation into Cancer and Nutrition
ERSPC	the European Randomized Study of Screening for Prostate Cancer
FDA	United States Food and Drug Administration
fPSA	free PSA
GnRH	Gonadotropin releasing hormone
GS	Gleason score
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases in Oncology
ICR	Icelandic Cancer Registry
IGF	Insulin-like growth factor
ISUP	International Society of Urological Pathology
NCCN	National Comprehensive Cancer Network
NPCR	The National Prostate Cancer Register in Sweden
PC	Prostate cancer
PLCO	the Prostate, Lung, Colorectal and Ovary trial
PSA	Prostate specific antigen
RP	Radical prostatectomy
RERs	Relative excess mortality rate ratios
RR	Relative risk
RS	Relative survival
RT	Radiotherapy
SCR	Swedish Cancer Register
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
tPSA	total PSA
TURP	Transurethral resection of the prostate
TVP	Transvesical prostatectomy
UICC	International Union Against Cancer
USA	United States of America
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization
WW	Watchful waiting
%PSA	Percentage of free PSA

LIST OF FIGURES

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LIST OF ORIGINAL PAPERS

The thesis is based on the following original manuscripts, which are referred to in the text by their Roman numerals (I-V)

I. Brasso K, **Ingimarsdóttir IJ**, Rusch E, Engholm G, Adolfsson J,Tryggvadóttir L, Jónsson E, Bill-Axelson A, Holmberg E, Storm HH. Differences in survival from prostate cancer in Denmark, Iceland and Sweden. Eur J Cancer 2013;49:1984-1992.

II. **Ingimarsdóttir IJ**, Rusch E, Grauers-Willadsen T, Engholm G, Storm HH, Jónsson E, Sigurðsson H, Tryggvadóttir L, Brasso K. Clinical aspects at the time of diagnosis of localized prostate cancer – a descriptive study of a Danish and an Icelandic cohort. *Submitted manuscript.*

III. Brasso K, **Ingimarsdóttir IJ**, Thomassen L, Friis S, Iversen P. Prostatacancer i Danmark 1943-2002. Danish Medical Bulletin 2007 Jan 8;169(2):129-32.

IV. **Ingimarsdóttir IJ**, Rusch E, Engholm G, Storm HH, Brasso K. Quality assessment of prostate cancer reports to the Danish Cancer Registry. Acta Oncol. 2016;55(1):24-29

V. Berg KD, Thormsen FB, Mikkelsen MK, **Ingimarsdóttir IJ**, Hansen RB, Kejs AM, Brasso K. Improved survival for patients with de novo metastatic prostate cancer in the last 20 years. Eur J Cancer 2016 Dec 23;72:20-27. doi:10.1016(j.ejca.2016.11.025. (Epub ahead of print).

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DECLARATION OF CONTRIBUTION

Paper I

On Danish and Icelandic Data

Engholm, Storm, and Tryggvadottir decided to participate in the European study named EUROCARE. A clinical information questionnaire was constructed by Ingimarsdóttir, Engholm, Brasso, and Iversen. A manual on how to gather and code clinical information was written by Ingimarsdóttir. Clinical data was gathered and processed by Ingimarsdóttir and Grauers-Willadsen. Statistics were mostly by Rusch.

On Swedish Data

Data was accessed from 2 Swedish regional databases of the NPCR. This was recorded by Rusch and Ingimarsdóttir with assistance from Adolfsson and Holmberg.

Written by Brasso and Ingimarsdóttir. Adolfsson, Bill-Axelson, Holmberg, Jónsson, Engholm, Storm, Tryggvadóttir and Rusch critically revised the draft and gave approval for the manuscript to be published.

Paper II

Designed by Ingimarsdóttir. A clinical information questionnaire was constructed by Ingimarsdóttir, Engholm, Brasso and Iversen. A manual on how to gather and code clinical information was written by Ingimarsdóttir. Clinical data was gathered and processed by Ingimarsdóttir and Grauers-Willadsen. Statistics were mostly by Rusch.

Written by Ingimarsdóttir. All work was done with supervision from Brasso and Sigurdsson. Brasso, Sigurdsson, Engholm, Storm, Tryggvadóttir, Grauers-Willadsen and Rusch critically revised the draft and gave approval for the manuscript to be published.

Paper III

Designed by Brasso, Ingimarsdóttir, and Friis. *Written by* Brasso and Ingimarsdóttir. Statistics done by Lars Thomassen. Critically revised by Friis and Lars Thomassen and given approval for publication.

Paper IV

Designed by Ingimarsdóttir. A clinical information questionnaire was constructed by Ingimarsdóttir, Engholm, Brasso and Iversen. A manual on how to gather and code clinical information was written by Ingimarsdóttir. Clinical data was gathered and processed by Ingimarsdóttir and Grauers-Willadsen. Statistics mostly by Rusch.

Written by Ingimarsdóttir. All work was done with supervision from Brasso and Sigurdsson. Brasso, Sigurdsson, Engholm, Storm, Tryggvadóttir and Rusch critically revised the draft and gave approval for the manuscript to be published.

Paper V

Designed by Berg. Clinical information on the historical cohort was gathered and processed by Ingimarsdóttir and Grauers-Willadsen. Clinical information on the contemporary cohort was gathered and processed by Berg. *Written by* Berg. *Critical revision by* Ingimarsdóttir.

Chapter 1: General introduction and outline of the thesis

INTRODUCTION

Following the introduction of prostate specific antigen (PSA), most Western countries face an epidemiologic shift in prostate cancer (PC) incidence. The disease spectrum has developed from being primarily composed of patients with symptomatic and more aggressive disease to a growing burden of cases with asymptomatic and often indolent disease. Good-quality epidemiological research is imperative to understand the nature of PC and is an important factor in predicting future development. All the Nordic countries have population-based cancer registries, founded between 1942 and 1958. The registries have long-time data available. Thereby, these registries are a favourable platform to investigate trends of PC incidence, mortality, and survival.

At the initiation of PSA testing, Nordic countries differed in their approach towards early case finding. Comparison of Nordic cancer register data showed large differences in PC incidence in the 1990s, whereas mortality rates were similar during that time. Large differences were also observed in relative PC survival, with the poorest outcome in Denmark. Currently, the differences in incidence between the Nordic countries have diminished.

To look for answers to the observed differences in both incidence and relative survival in the last 30 years, we decided to gather clinical data and study the main characteristics of patients diagnosed in the early days of PSA-testing and observe their outcome after more than ten years of follow-up.

BACKGROUND

The prostate

Anatomy

The prostate gland is a part of the male reproductive system located in the retroperitoneum below the urinary bladder and surrounding the bladder neck and the urethra. It is oval-shaped and for men under the age of 50, it is approximately the size of a walnut and weighs around 20g. The growth and development of the gland is androgen-dependent.(1) A thin capsule surrounds the gland, consisting of an inner layer of smooth muscle and an outer layer of collagen.(2) It is not a well-defined anatomical structure, as it is more evident along the base but less so along the anterior and apical surfaces.(3) Under the thin capsule, the prostate consists of ducts and acini with secretory epithelium, basal cells and scattered neuroendocrine cells supported by fibroelastic stromal tissue that has randomly oriented bundles of smooth muscle. The secretory epithelium is located on the luminal side of the gland and secretes prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP).(4) Two ejaculatory ducts from each testicle merge into the prostatic urethra.

The gland is divided into 3 zones: central, peripheral and transition zones, Figure 1.(5) The central zone is a cone-shaped area that consists of about 25% of the whole gland. It surrounds the ejaculatory ducts and is located in the most anterior part of the gland, which makes tumours that originate there difficult to palpate.(2) Only about 2.5% of PC originates from there but, it tends to be more aggressive and more likely to invade seminal vesicles.(6) The peripheral zone is the dorsal part of the gland and makes up approximately 70% of the prostate. Most prostate cancers are found in this zone, and it is the part of the gland most easily felt by digital rectal examination (DRE). A median furrow divides the peripheral zone into right and left lobes, often described by DRE.(5, 7) The transition zone is between the 2 other zones. It surrounds the urethra and constitutes the remaining 5% of the prostate volume.

The transition zone and the anterior fibromuscular stroma often enlarge to massive size in benign prostate hyperplasia (BPH). Thus, another division that better correlates with the pathological and physiological aspects of the prostate are an inner periurethral zone (the transition zone) that is the primary site for BPH and rare carcinomas arising from large ducts, and an outer cortical zone (the central and peripheral zones) where adenocarcinoma arises from peripheral ducts and acini.(4)

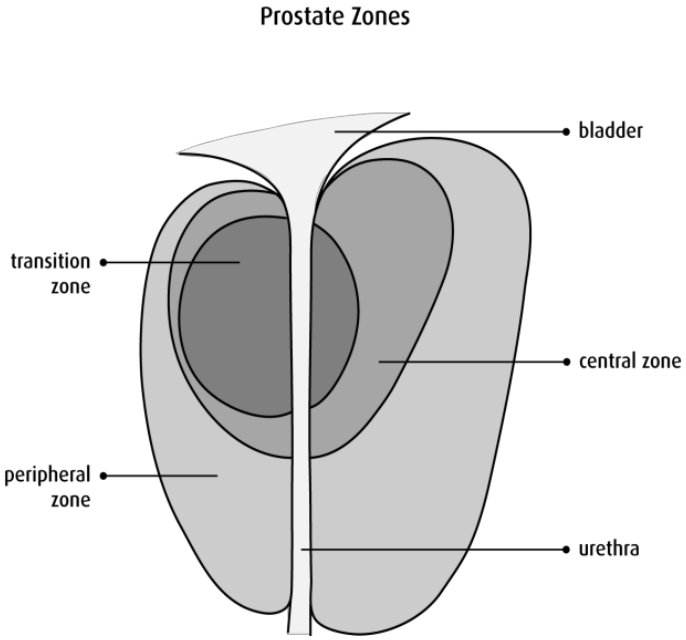


Image from the Canadian Cancer Society, Prostate zones. Retrieved online from www.cancer.ca on October 17th 2016. All rights reserved.

Figure 1: The prostate gland is divided into 3 zones: the peripheral, transition, and central zones.

Physiology

The main function of the prostate gland is to produce and secrete the thin, slightly-alkaline fluid that facilitates semen liquefaction. The fluid is made continuously and is rich in proteins and minerals that maintain and nourish sperm. The muscle fibres are wrapped around the urethra and are under involuntary nervous system control.(7) These fibres can contract to slow and stop the flow of urine and thus play a part in controlling the flow of urine.

Lower urinary tract symptoms (LUTS)

As men age, the prostate gland usually increases in size, a condition referred to as benign prostate hyperplasia (BPH).(8) In the aging prostate, histopathologic, hyperplastic changes are mediated by circulating and intraprostatic androgens.(9) Mainly, the transition zone enlarges and ultimately becomes the largest part of the prostate and pushes the peripheral zone further back towards the rectum.(2) BPH may cause lower urinary tract symptoms (LUTS), i.e. urinary symptoms (frequency, nocturia, urgency, and dysuria) and bladder outlet obstruction (difficulty starting and maintaining a steady stream of urine).(8) These symptoms may coincide with PC, since incidence of BPH as well as the malignancy increases with age. Both BPH and PC depend on androgens to grow, and both respond to androgen deprivation therapy. However, no causal relationship has been established between BPH and PC.(10)

Prostate specific antigen (PSA)

PSA is a glycoprotein that is a kallikrein-like protease (11) and is expressed in both normal and malignant prostate cells.(12) PSA is expressed in nearly all types of prostate cancers. Its level of expression may vary within the tumour (tumour heterogeneity), especially in very poorly differentiated prostate cancers, where it can be lower than in normal prostate epithelium.(13)

Serum PSA increases with age, and PSA and prostate volume have an age-dependent log-linear relationship. Some patients with BPH have a slightly elevated PSA, and a large proportion of cases with clinically localised PC may have a PSA value within the normal range.(10) The exact threshold where PSA value is considered elevated is highly controversial, but historically, a concentration above 4 ng/mL has been considered abnormal in most. The most common explanation for an elevated PSA is BPH because of the very high prevalence of this condition in men over the age of 50.

PSA testing has increased exponentially the early detection of PC in the United States and Western Europe. PSA is not cancer-specific, but the absolute value of serum PSA can be useful for determining the extent of PC and assessing the response to PC treatment.

Serum PSA levels overlap considerably in men with BPH and those with PC. Prostatitis (with or without active infection), rectal exploration (although the increase is not clinically relevant) or instrumentation of the prostate, prostate biopsies, and acute urinary retention can also cause an elevation of PSA levels.(14, 15) These elevations should be transitory and resolve with proper treatment.

For patients with localised PC followed by active surveillance, certain dynamic PSA measurements, e.g. PSA velocity and PSA doubling time, are commonly used to alert clinicians about a rapidly rise in PSA level.(16) Free PSA (fPSA) is unbound and is expressed as a ratio of total PSA (tPSA). The percentage of serum fPSA (%fPSA) has been shown to be significantly lower in PC patients than healthy individuals. A study from 1998 showed that a 25% fPSA cut-off detected 95% of PC cases while avoiding 20% of unnecessary prostate biopsies.(17) It is unclear whether PSA density (PSA level as a function of prostatic volume) can provide a more cancer specific test.(18)

A noncoding prostate specific RNA called PCA3 is over-expressed in PC patients. Urine samples acquired post-DRE can be assayed to quantify PCA3 overexpression and the result can be useful in determining which patients should undergo a repeat biopsy of the prostate.(19)

Prostate cancer (PC) - Histology

Approximately 95% of prostate cancers (PC) are adenocarcinomas.(2) The remaining few percentages include clear cell carcinomas, ductal carcinomas, intralobular acinar carcinomas, mucinous carcinomas, and small-cell tumours.(20) Adenocarcinoma of the prostate is rare in patients under the age of 40 years, but for men older than age 40, the incidence rises quickly. Autopsy-based prevalence is 80% by age 80 years.(21) Despite wide variation in the incidence of clinically apparent adenocarcinoma, the prevalence of clinically occult cancer is similar in different geographic and ethnic groups.(2)

PC has a variable natural history and can frequently be indolent, even in the setting of watchful waiting.(22) One study suggests that more than 97% of men with low-risk prostate cancer (LRPC) are likely to die of other causes.(23) Some forms are more prone to spread beyond the gland,(24) and this correlates with the tumour grade. The most common sites of metastases are lymph nodes and bone.(2, 25)

Histological grade can be recorded based on the WHO-grading system (26) or by Gleason score system.(27) The WHO-grading system takes into account the degree of glandular differentiation and the extent of nuclear anaplasia (variation of nuclear size, shape, chromatin etc.) is graded from being slight/low (Grade I), moderate (Grade II) or marked/poor (Grade III).(28) Since 1999, the Gleason score system has been internationally recognized as the standard for PC grading.(29)

The Gleason score grading system is based on low-power microscopic evaluation of the degree of glandular architectural differentiation and the growth pattern of the tumour in relation to the stroma. The Gleason score consists of adding the two most predominant tumour patterns, each of which is graded from 1 to 5, where tumour pattern 1 is the least aggressive and 5 is the most aggressive.(24) A tertiary pattern is found in some tumours and this is only reported if the grade is 5.(30, 31)

In 2005 and again in 2014 the International Society of Urological Pathology (ISUP) upgraded the Gleason grade classification.(32, 33) In 2005 the biopsy specimens the score was changed to be the sum of the most predominant pattern and the most aggressive pattern, and if they were one and the same a second lower pattern was chosen as the second pattern. Regular cribriform glands, previously classified as tumour pattern 3, were graded as pattern 4 and this led to an increased proportion of tumour pattern 4.(34) In 2014 several new modifications were accepted that provided more accurate stratification of tumours and simplified the number of grading categories.(33)

Prostate cancer - Staging

Early stages of PC are usually asymptomatic.(2) The extent of the spread of PC (staging) is assessed by the Tumour Node Metastases (TNM) classification developed and maintained by the Union for International Cancer Control (UICC) (Table 1).(35) Staging is schematically presented in Figure 2.

TNM Clinical Classification		
T – Primary Tumor		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Clinically inapparent tumor, neither palpable nor visible by imaging
	T1a	Tumor incidental histological finding in ≤ 5% of tissue resected
	T1b	Tumor incidental histological finding in > 5% of tissue resected
	T1c	Tumor identified by needle biopsy, e.g. because of elevated PSA
T2		Tumor confined within prostate
	T2a	Tumor involves ≤ 50% of one lobe
	T2b	Tumor involves > 50% of one lobe, but not both lobes
	T2c	Tumor involves both lobes
T3		Tumor extends through the prostatic capsule
	T3a	Extracapsular extension (uni- or bilateral) including microscopic bladder neck involvement
	T3b	Tumor invades seminal vesicles(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles; external sphincter, rectum, levator muscles, and/or pelvic wall

Table 1:TNM clinical classification according to the UICC.(35)

Grade is included among other prognostic factors (e.g. age, comorbidity, clinical stage, and PSA level) in therapeutic decision making. Cancers with a poor WHO score and a high Gleason score tend to be more aggressive and carry a worse prognosis. Differentiation of PC by Gleason score is the strongest predictor for progression and prostate cancer-specific death.(36, 37)

According to McNeal, the Gleason score system can stratify adenocarcinomas into 3 subgroups according to different stages of aggressiveness: 1) Gleason grade 1 and 2, almost always small (<1cm^3), indolent, localised, and most often confined to the transitional zone; 2) Gleason

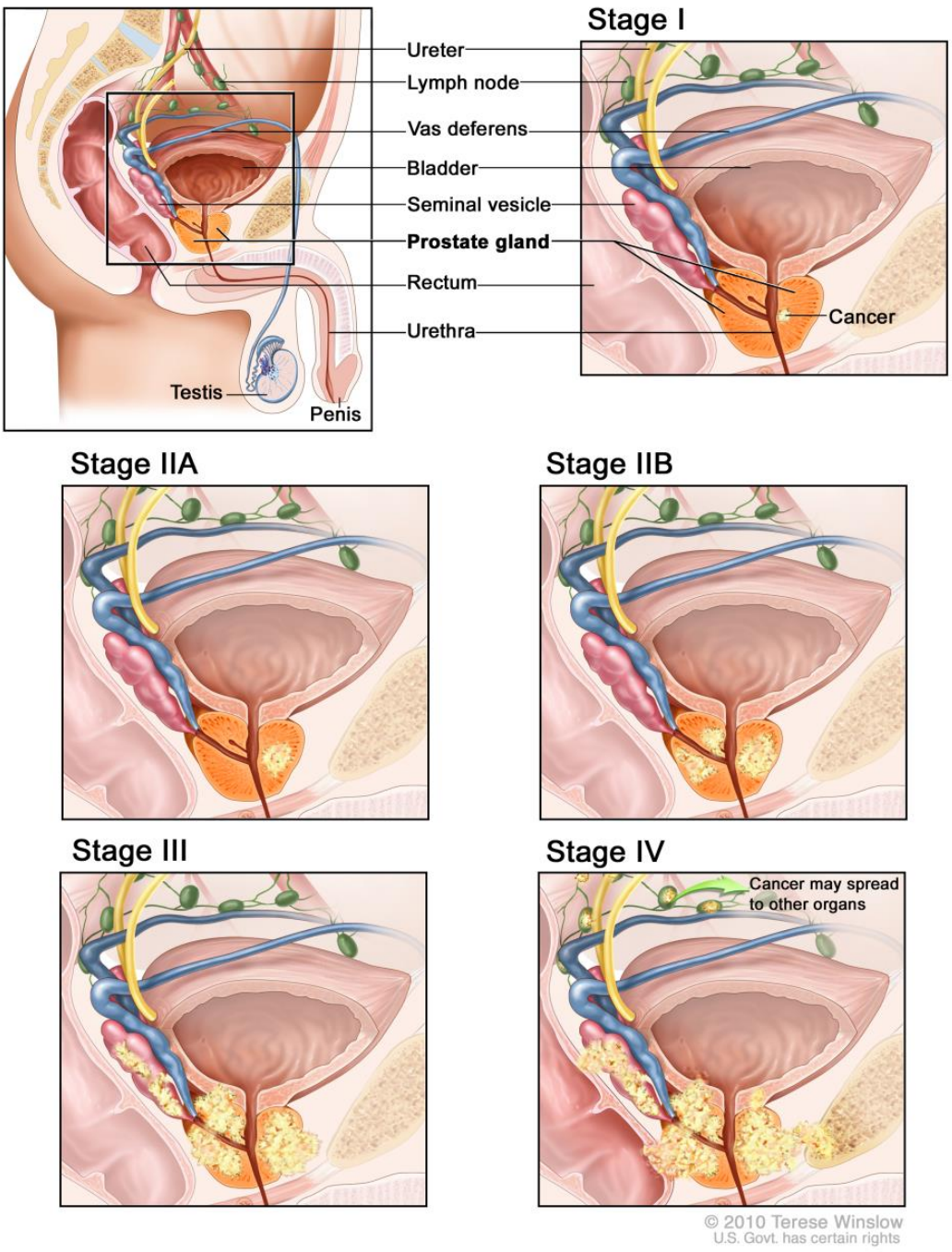


Figure 2:. Schematic illustration of the different stages of prostate cancer. Stage I, where the cancer is too small to be felt on digital rectal examination (DRE), but is discovered through prostate biopsy or TURP. Stage II, where the tumour is large enough to be palpable by DRE, but is confined to the gland. Stage III, where the tumour has spread outside the gland and may have invaded the seminal vesicles. Stage IV, with spread to surrounding tissue, e.g. bladder, rectum, or the pelvic muscles.

grade 3, very common and variable in size; 3) Gleason grade 4 and 5, larger and more aggressive than lower-grade tumours and more likely to extend beyond the prostate and metastasise.(24) In clinical practice this stratification has more or less been replaced by regarding risk categories. The classifications of risk categories vary remotely between different research centres.

Bratt et al. used the following classification: i) Low-risk PC is having T1-2, Gleason score ≤ 6, PSA < 10 ng/ml, N0/NX and M0/MX. ii) Non-low risk is defined as any cancer not in the low-risk group that has Gleason score ≥ 7, and/or T3-T4, and/or PSA > 10 ng/ml, and/or N1 and and/or M1. iii) The high-risk group has Gleason score ≥ 8, T3-T4, PSA ≥ 20 ng/ml and N1 and/or M1.(38)

According to the National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2017 the risk categories are the following: i) Very low risk with stage T1c, Gleason score ≤ 6, PSA < 10 ng/ml, presence of disease in < 3 biopsy cores, ≤ 50% PC involvement in any biopsy core and PSA-density ≤ 0.15 ng/ml/g. ii) Low risk are stage T1-T2a, Gleason score ≤ 6 and PSA < 10 ng/ml. iii) Intermediate risk are patients with stage T2b-T2c, Gleason score 7 or PSA 10-20 ng/ml. iv) High risk patients have stage T3a, Gleason score 8-10, or PSA > 20 ng/ml. v) Very high risk patients (locally advanced) are defined as cases with stage T3b-T4, primary Gleason pattern 5, or more than 4 biopsy cores with Gleason score 8-10.(39)

Ohmann et al. defined 5 risk categories, which were similar to the NCCN's guidelines but were further modified to distinguish between regionally metastatic and distant metastatic dispersion; i) Low risk localised: stage T1-T2, Gleason score ≤ 6 and PSA < 10 ng/ml. ii) Intermediate risk localised: stage T1-T2, Gleason score 7 (3+4 or 4+3) and/or PSA 10-20 ng/ml. iii) High risk localised: T3 and/or Gleason score 8-10 and/or PSA 20-50 ng/ml. iv) Regionally metastatic (locally advanced): stage T4 and/or stage N1 and/or PSA 50-100 ng/ml without distant metastases (stage M0 or MX). v) Distant metastatic: stage M1 and/or PSA ≥ 100 ng/ml.(40)

Prostate cancer – Risk factors

Only age, sex, and race have been established as risk factors for prostate cancer.(41) A genetic component can contribute to the risk of developing PC,(42) consistent with associations with family and race (predominantly black race).(42) Both incidence and mortality of PC is higher among African American men than Caucasian men.(43, 44) Higher incidence rates in black populations in the Caribbean and in Africa, where PSA testing is uncommon, points to a genetic disposition to develop PC.(45) Autopsy studies have shown that PC can transform into aggressive forms earlier in African-American than Caucasian men.(46)

Genetics Overview

Having a first-degree relative (father or brother) with PC increases the risk of developing the disease approximately two- to three-fold,(47), but as much as a ten-fold increase in risk has been reported in men having 3 or more first- or second-degree affected relatives.(48, 49) In a study among 203,691 pairs of Scandinavian twins, 57% heritability (the proportion of susceptibility to cancer that was accounted for by genetic defects) was observed for PC.(50) A study in 2000 found that the time interval between the diagnoses of PC was significantly shorter for concordant pairs of monozygotic twins than that for concordant pairs of dizygotic twins (5.7 vs. 8.8 years).(51)

X-linked and both autosomal dominant and recessive patterns of inheritance have been found in families with multiple cases of PC.(52) A specific HOXB13 mutation has been identified in approximately 2-5% of PC patients who have origin in Northern Europe.(53, 54)

The BRCA2 gene on chromosome 13 is associated with female and male breast cancer, and in 1997, an Icelandic paper showed a clustering of PC in some of the Icelandic BRCA2 families studied.(55) Further, all of the Icelandic BRCA2 carriers who developed PC had an advanced disease that was the main cause of death.(55) Since then, a number of studies have confirmed an increased risk of PC among male carriers of either BRCA1 or BRCA2 mutations in the setting of hereditary breast/ovarian cancer or early-onset prostate cancer.(56-59) Several other studies have suggested that BRCA1/2 carriers are more prone to develop more aggressive forms of PC that more commonly develops at a younger age.(60, 61) Therefore, the BRCA1/2 mutation seems to be both a predictive and prognostic factor for PC.(55, 60, 61) Lynch syndrome has a 2- to 5-fold increase in for developing PC due to germline mutations in MLH1, MSH2, MSH6, PMS2 or EPCAM.(62, 63)

Since the onset of the “PSA era” more relatives of men with recently diagnosed PC have been PSA tested leading to a familial aggregation of cases, often with clinically insignificant low-risk PC.(64) This has led to inflation of the cancer risk for men with a family history of PC.(64, 65) The probability of being diagnosed with any type of PC (low, non-low and high-risk) increases with age and the number of affected family members.(38) For the majority of men aged of 75 years with a family history of PC the probability of being diagnosed with PC themselves was between 30-60%, where around half of the group would be in the low-risk category with little clinical significance. The probability of high-risk PC was one-sixth to one-fourth of the probability of any PC.(38)

Environmental Factors

The fact that the incidence of PC has increased already in the first to second generation after migration from a low-incidence to a high-incidence area points towards the importance of exogenous factors in developing PC.(66) The evidence of milk and dairy product consumption has been considered limited suggestive in an increased risk of developing PC. Monounsaturated fatty acids have been shown to have a significant positive association with the risk of PC, while no association has been found between PC and energy intake from saturated fat. Polyunsaturated fatty acids have shown a non-significant protective association. Foods containing lycopene, i.e. tomatoes have shown a non-linearity protection for developing total PC ($p<0.01$) but not for advanced disease ($p=0.12$). Serum alpha-tocopherol decreases the risk of developing PC. The association of calcium and risk of PC have been inconclusive, but dietary calcium probably increases the risk.(67)

In 2014 the European Prospective Investigation into Cancer and Nutrition (EPIC) evaluated the risk of developing PC with exposure of several nutritional and hormonal factors. The strongest association for the risk for PC was with insulin-like growth factor (IGF)-1, where the risk was higher in men with high IGF-1 levels compared to men with low levels (OR 1.69 (1.35-2.13)), without signs of heterogeneity by grade or stage at diagnosis. The risk of developing PC was, however, not associated with IGF-binding protein-3.(69) Testosterone is an important regulator of insulin sensitivity in men and testosterone levels have been shown to be low in men with diabetes, visceral obesity (which is strongly associated with insulin resistance), coronary artery disease and metabolic syndrome. Hypotestosteronaemia, in patients treated with androgen deprivation therapy, may have a role in the pathogenesis of insulin-resistant states with higher IGF-1 and therefore perhaps increasing the risk for PC.(69)

Prostate cancer epidemiology

Cancer registries

The Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) are geographically, historically, and culturally related. Each country has a population-based cancer registry and the notification of a cancer diagnosis is mandatory. The Danish Cancer Registry (DCR) was founded in 1942 and is the oldest nationwide population-based cancer registry in the world.(70) The Finnish, Icelandic, and Norwegian registries were founded between 1952 and 1954, and the Swedish Registry was founded in 1958. All 5 Nordic countries have personal identification numbers, and the registries are population-based. Peer-reviewed journals have reported close to 100% coverage of incident cases in each of the Nordic registries.(71-76) Incidence figures in the DCR are available from January 1st 1943 and from the Icelandic Cancer Registry (ICR) from January 1st 1955.

Reporting the TNM stage to the DCR and Swedish Cancer Registry has been mandatory since 2004 and 2003, respectively, but the information has not yet been validated. Since 1998, the ICR has requested physicians reporting patients with prostate cancer to also report the TNM stage. However, reporting first became mandatory in 2007, and has not been validated.

The Association of the Nordic Cancer Registries (ANCR) has constructed a database (NORDCAN) on cancer incidence, mortality, prevalence, and survival statistics of the 50 major cancers in each of the Nordic countries. The NORDCAN database is an easily accessible and comprehensive graphical and statistical tool that has been available online (www.ancr.nu) since 2002.(77)

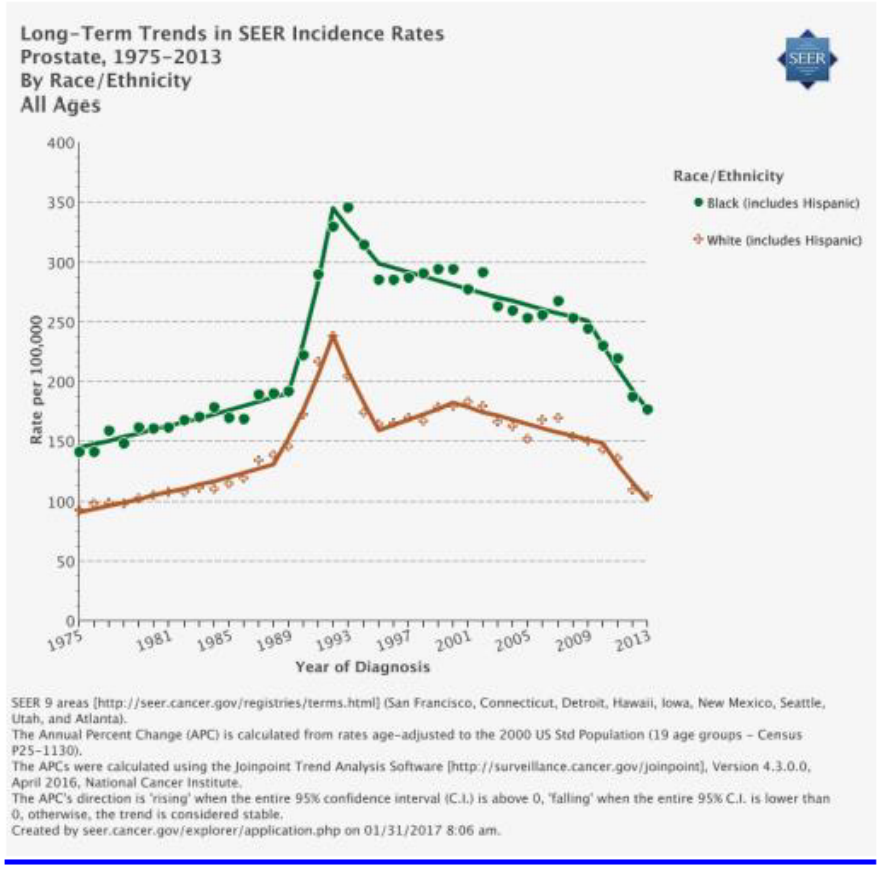
Trends in incidence and mortality

International Trends

Internationally, the incidence of PC has varied considerably. Today PC is the second most common cancer in men worldwide (after lung cancer), but is the most common cancer in developed regions.(78) The highest incidence has, throughout the last decades, been observed in Northern America, Northern and Western Europe, Australia, and New Zealand.(78-80) In certain developing regions, e.g. the Caribbean, South America, and sub-Saharan Africa, incidence rates are also relatively high.(78) According to recent data looking at 43 different populations around the world, the lowest annual age-specific incidence rates were found in Asia.(42)

Opportunistic PSA-based screening began in the United States in the mid-late 1980s (81) and was further strengthened in 1991 and 1992 after a study pointing to the usefulness of PSA testing as a screening tool for PC was published.(82) In 1994 the United States Food and Drug Administration (FDA) approved the use of the PSA test for detecting PC and since then widespread PSA-based screening began in the United States.(83) PC incidence in the United States more than doubled between the mid-1980s and the 1990s (84)(Figure 3), with similar trends appearing several years later in the Nordic countries.(85) The rise was attributed to an increase in diagnostic procedures, first and foremost PSA testing amongst asymptomatic American men.(86, 87) In 2001, over 80% of men older than 70 years of age in the United States reported to have had a PSA test performed.(88) PC is currently the most common noncutaneous malignancy in the United States and is the third only to lung and colorectal cancer as a leading cause of cancer death.(89)

Incidence rates peaked in 1992 among Caucasian men, with 238.2 cases per 100,000 and the following year for African Americans, with 344.1 cases per 100,000. Between 1992-1995, incidence rates started to fall sharply by about 12% per year. This sharp decline was believed to be a result of a marked decline in the number of first-time PSA testing of American men.(90) Thereafter, incidence rates reached a plateau between 1995-2000 and decreased annually by about 2% from 2000-2006.(91) The decrease was most evident among men aged 75 years or older but also fell substantially among men between 65-74 years of age. For the youngest group, between 50-64 years old, the increase in incidence was initially sharp to around 1992, then continued at a slower pace from 2002 but began to fall around 2008 to 2009 (see Appendix 1, figures 1-3). Between 2008-2012, the incidence was 123.0 per 100,000 for Caucasian men and 208.7 per 100,000 for African American men. In 2016, a total of 180,890 new cases and 26,120 deaths are estimated.



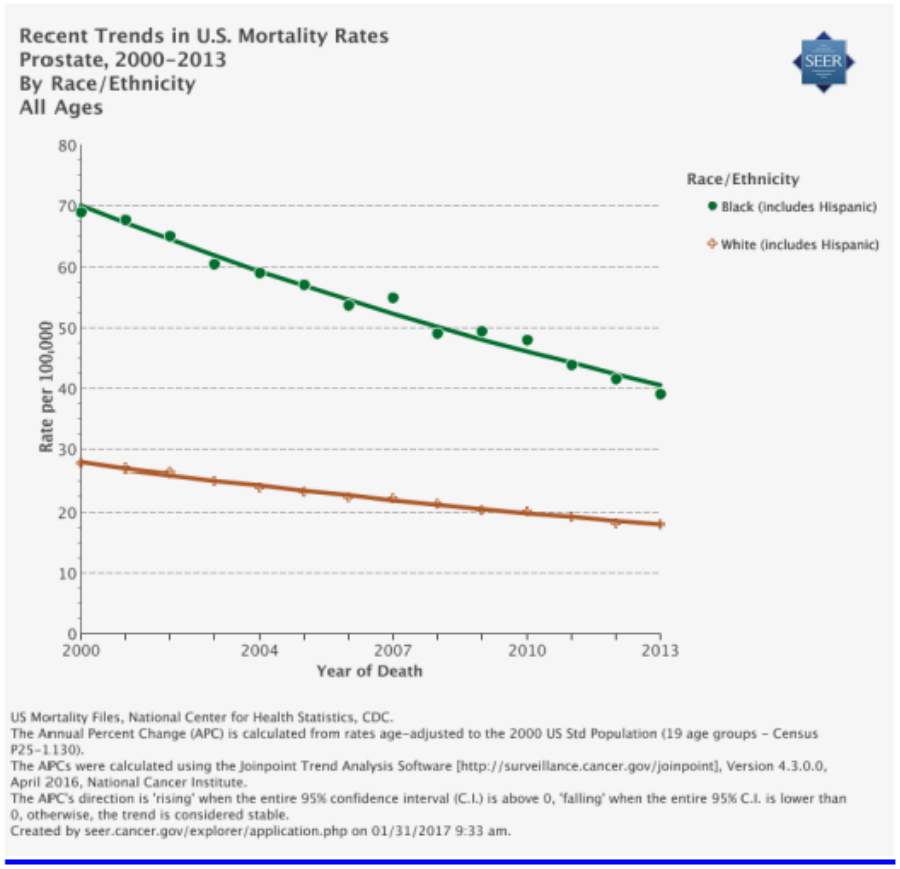


Figure 3: Age-adjusted prostate cancer incidence and mortality rates per 100,000 for African American and Caucasian Americans between 1975 and 2013 as measured in 9 areas of the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program. Data is age-adjusted to the year 2000 population standard.

Advanced PC was more commonly seen among African American men in the early nineties compared to rates amongst Caucasians but has decreased since the mid-nineties for both races and is now similar. Stage T2 PC increased rapidly in the early nineties amongst American cases, especially amongst African American men. Rates then levelled off, but have been decreasing for both races since around 2002. The number of stage T1 cancers has gradually increased from around 1993. This shows a clear stage migration from advanced to a more indolent disease pattern (Figure 4). Most American PC patients have clinically localised tumours at diagnosis.(92)(see Appendix 1 figures 7-10).

Less variation is observed in mortality rates worldwide, ranging from 1-30 per 100,000 inhabitants.(80) In black populations, i.e. in the Caribbean and sub-Saharan Africa, mortality rates are generally high. Mortality rates are intermediate in Europe and Oceania, and very low in Asia.(78) In the United States, mortality rates increased by 3% between 1987-1991, remained unchanged from 1991-1994, but decreased by about 4% per year in the time period 1994-2006.(91) The fall in mortality rate in the U.S. was primarily in men aged 75 years and older but observed in all age groups (see Appendix 1, figures 4-6). The fall in mortality rate has been attributed to several factors, e.g. positive effects of treatment and possibly earlier diagnosis,(42) more changes in attribution of cause of death, effects of androgen deprivation therapy (ADT) for advanced disease, and even a rise in risk of death due to side-effects of ADT, e.g. risk of fractures, diabetes, coronary heart disease,(69, 93, 94) myocardial infarction and even sudden cardiac death.(95-97)

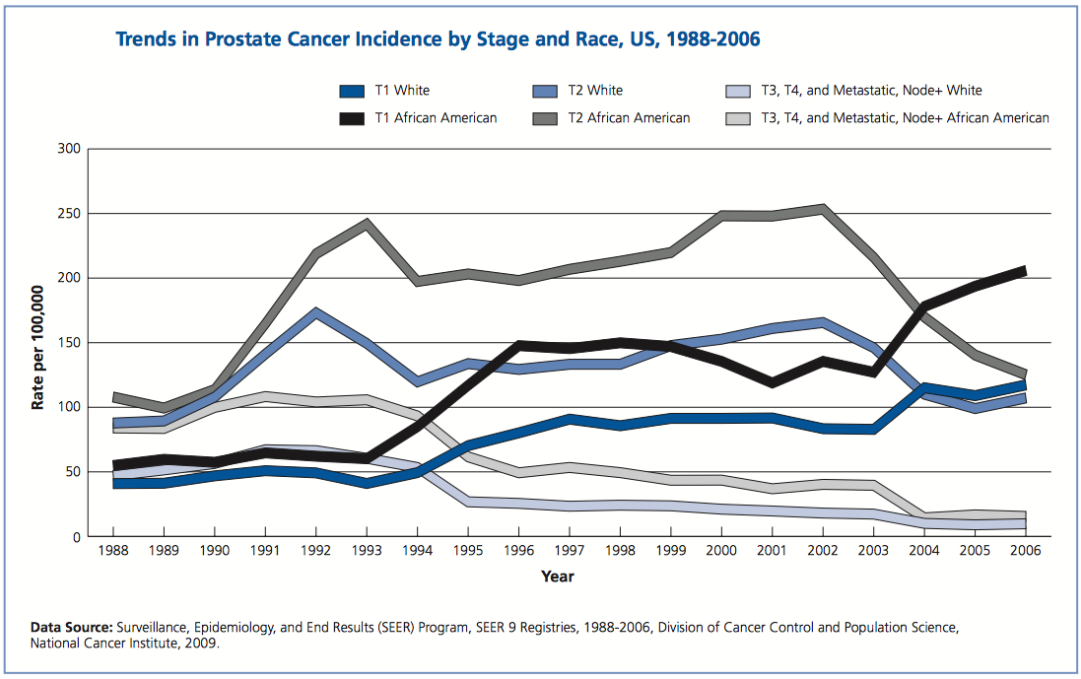


Figure 4: Trends in incidence rates per 100,000 by stage for Caucasian and African American cases in the time period 1988 to 2006.

Incidence Trends in the Nordic Countries

Similar to many Western countries, the incidence of PC in Iceland has risen considerably over the last 3 decades (Figure 5). From 1955 to 2013, a total of 5774 Icelandic PC cases were reported to the ICR, increasing from 69 cases in the period 1955-1959 to 1005 cases in the period 2009-2013.(77)

In the 1990s, Danish physicians were generally conservative about diagnosing PC among asymptomatic men, mainly reflected by less-frequent use of PSA testing.(98, 99) This resulted in fewer diagnosed cases compared to neighbouring countries. Prior to 1995, incidence rates had remained relatively stable around 70 per 100,000 Danish men, but thenceforth a rise in incidence was seen in Denmark. In August 1995, radical prostatectomy (RP) was first introduced in Denmark.(100) In the period 1995-2009, the rise in PC incidence was probably a reflection of increased frequency of PSA testing and further implementation of RP. From 1999 to 2008, the greatest average increase in incidence was observed in Denmark (about 8% per year), and the difference in incidence rates between Denmark and the other Nordic countries became less noticeable.(101)

From 1943 to 2013, a total of 70,299 Danish men were diagnosed and reported to the DCR. In the last 5-year period available, 2009-2013, a total of 21,929 patients were reported to the DCR.(77) In the study period, around 1997, PC was the most common cancer among men in Iceland and the third most common in Denmark. Today, it is the most common cancer in men in both countries, but lung cancer is still the leading cause of cancer death, followed by PC, in both countries

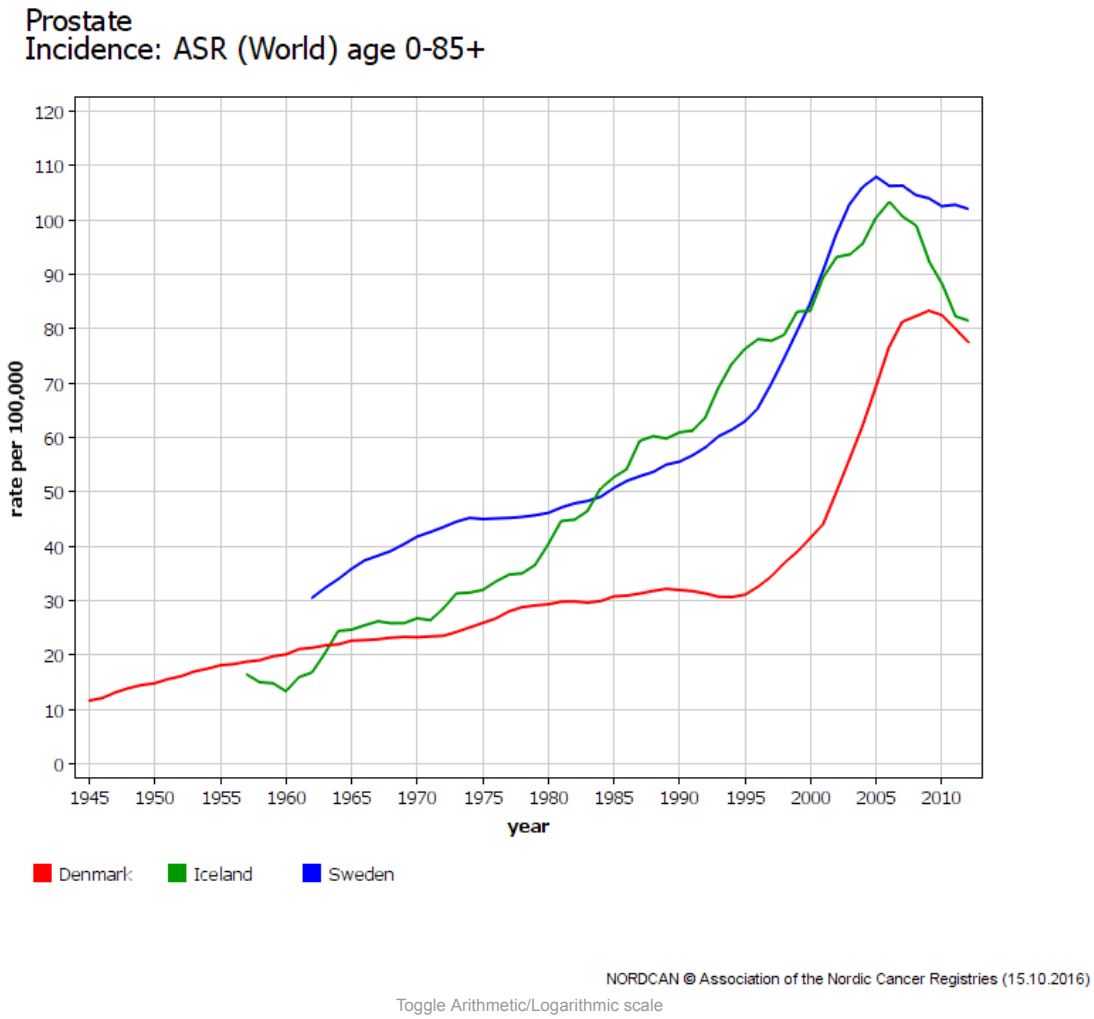


Figure 5: Trends in age-standardized (European) prostate cancer incidence in Denmark, Iceland and Sweden.

Mortality Trends in the Nordic Countries

Before the 1980s large fluctuations in mortality rates were observed, though with an upward trend. In the 1980s and through the mid-1990s, age-standardized PC mortality rates in all the Nordic countries remained strikingly similar.(77) In the mid-1990s, mortality rates increased slightly, but thereafter began to fall in all 5 countries. This reduction in mortality was most apparent in Finland, where it fell from about 18 to 13 per 100,000 in the time period 1996 to 2011, but the sharpest fall was seen from 2005 onwards. In Iceland, the rates fell from approximately 21 to 16 per 100,000 between 1997 and 2008. Comparable mortality rates between 1998 and 2011 were about 24 to 17 in Norway, 22 to 17 in Sweden and 20 to 18 per 100,000 person-years in Denmark.(77) Figure 6 shows that mortality rates in Denmark, Iceland, and Sweden have had a similar slowly falling trend since the turn of the century.

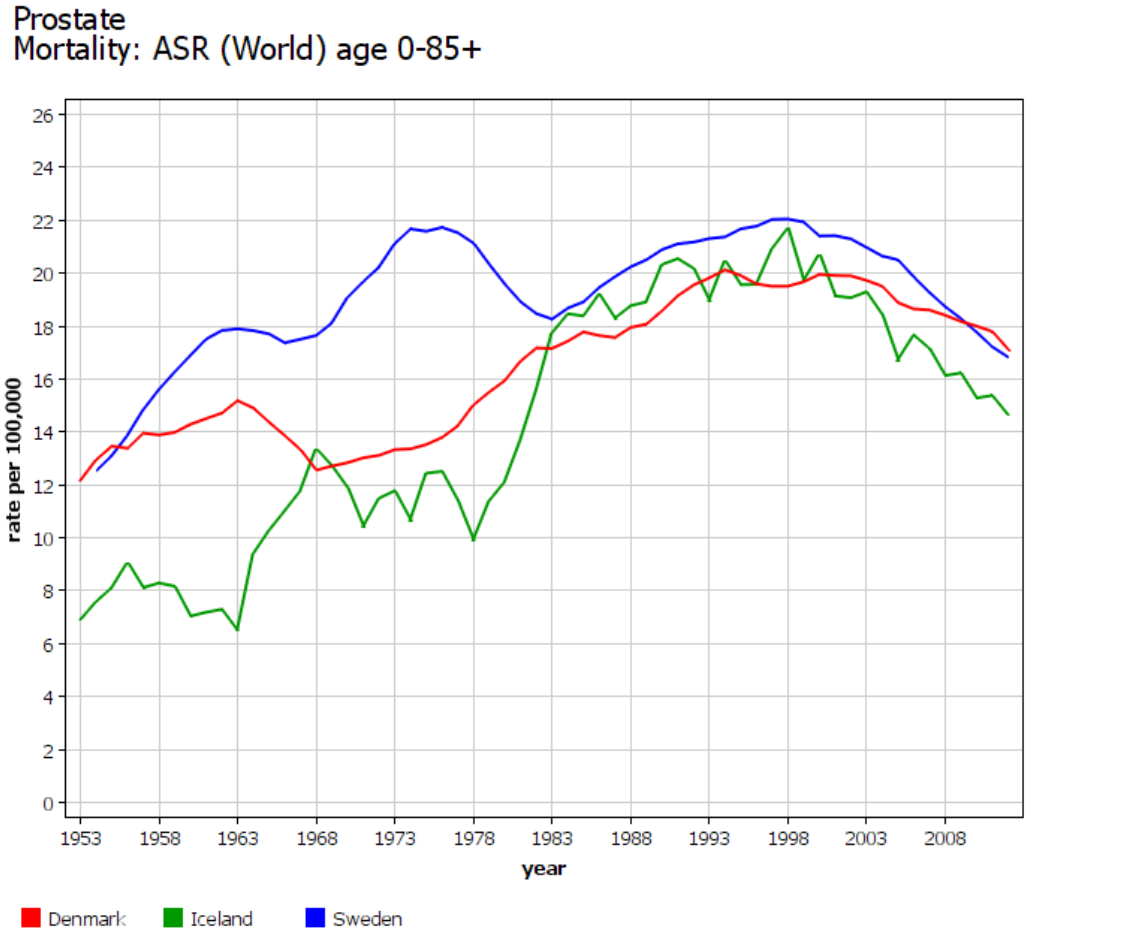


Figure 6: Trends in age-standardized (European) prostate cancer mortality rates in Denmark, Iceland, and Sweden.

Prostate Cancer Survival Trends in the Nordic Countries

The 5 Nordic countries together comprise about 25-million inhabitants. Bray et al. demonstrated large differences in relative survival and excess mortality following the diagnosis of PC within the Nordic countries, with Danish patients generally having the poorest prognosis.(102) The results were based on information gathered from population-based national cancer registries and were consistent with several earlier studies demonstrating poorer outcome in Denmark compared to other Nordic and European countries.(103, 104) However, the studies did not include clinical information.

Prostate cancer – screening trials and recommendations

None of the Nordic countries have yet recommended population-based screening programs for early-stage prostate cancer. The decision was further supported in 2009, when the results of 2 large randomized trials, the Prostate, Lung, Colorectal and Ovary trial (PLCO) in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC), in Europe, were published.

The PLCO trial randomized more than 76-thousand men in 10 U.S. study centres to either annual screening with a PSA test and digital rectal exploration (DRE), or standard care as the control group. They concluded that PC mortality in patients detected by screening was very low, and no significant difference in mortality was found between the 2 groups, even after 13 years of follow-up.(105, 106)

The ERSPC trial included over 162-thousand men who were randomized to a PSA test and DRE every 2-4 years or to a control group. Cumulative incidence in the screened group was approximately 8% compared to 5% in the unscreened control group, but the absolute risk difference was 0.71 deaths per 1000 men when followed up for 9 years.(107) However, after follow-up of 14 years of the Gothenburg section of the trial comprising 20 000 men a relative risk reduction of 50% in PC mortality was observed.(108)

In 2008 The United States Preventive Services Task Force (USPSTF) recommended against PSA screening of men over the age of 75 years.(109) In 2012 the USPSTF´s publication recommended against PSA screening for all age groups, but did not recommend against the use of the PSA test for surveillance after diagnosis or treatment for PC.(110)

In 2013, the American Urologic Association (AUA) issued guidelines regarding early detection of PC. They do not recommend screening of men under age 40 years, among men ages 40 to 54 years at average risk, or men older than 70 years with less than 10 to 15 years of life expectancy. For men ages 55 to 69 years and men younger than 55 years with higher risk (positive family history or African American race), decisions regarding screening should be individualized, weighing the benefits of preventing PC mortality in one individual in 1000 men screened over a decade against the potential harm of screening.(111)

Prostate cancer diagnostics and treatment in Denmark and Iceland: a historical perspective

The TURP Era

Prior to 1990, the increase in PC incidence was probably due to increased awareness of LUTS and easier access to medical expertise, but mainly due to a rise in the number of TURP procedures.(112) Because of a small total population, most Icelandic physicians must complete their specialist training abroad. Most Icelandic urologists receive their specialist training in Sweden or the U.S. Around 1970, a number of Icelandic urologists returned to Iceland and introduced the TURP procedure.

The need for TURP operations for BPH substantially decreased in the eighties and nineties with the introduction of medical therapy with 5-alpha reductase inhibitors and alpha-adrenergic blockers, as well as a more conservative approach towards operative interventions. The levelling of the rise in incidence in Denmark from 1991 to 1995 may be explained by a more conservative approach as well as a 20% decline in the number of TURP procedures in Denmark.(113, 114) During the 1990s, the incidence of PC uniformly increased in the majority of European countries, and incidence rates in Iceland and Sweden were among the highest in Europe.(115)

The PSA Era

Around 1990, PSA testing was introduced in the Nordic countries. A rapid increase in its use was thereafter observed (116, 117) in Iceland despite the fact that national authorities advised against opportunistic use of PSA testing, Figure 7.(118) The rise in PSA testing was followed by a sharp rise in PC incidence.(85) Annual PSA testing rates in Sweden rose three-fold from 1995 to 2002.(85)

A Danish publication may have caused PSA testing in Denmark to remain small-scale until around 1995.(98) The number of PSA tests within the normal range (less than 4 ng/ml) in general practice (GP) in Denmark increased from 201 tests in 1997 to 3411 tests in 2006. In the Danish hospital setting, the number of incidental PSA tests increased three-fold between 1997 to 2001 but fell slightly thereafter.(119) The sharp rise in PC incidence in Denmark is reflected by an increase in the number of patients with localised PC.(120) The incidence rate for localised PC in Denmark increased from 11.4 per 100,000 in 1993-1997 to 50.8 per 100,000 in 2008-2009.(120)

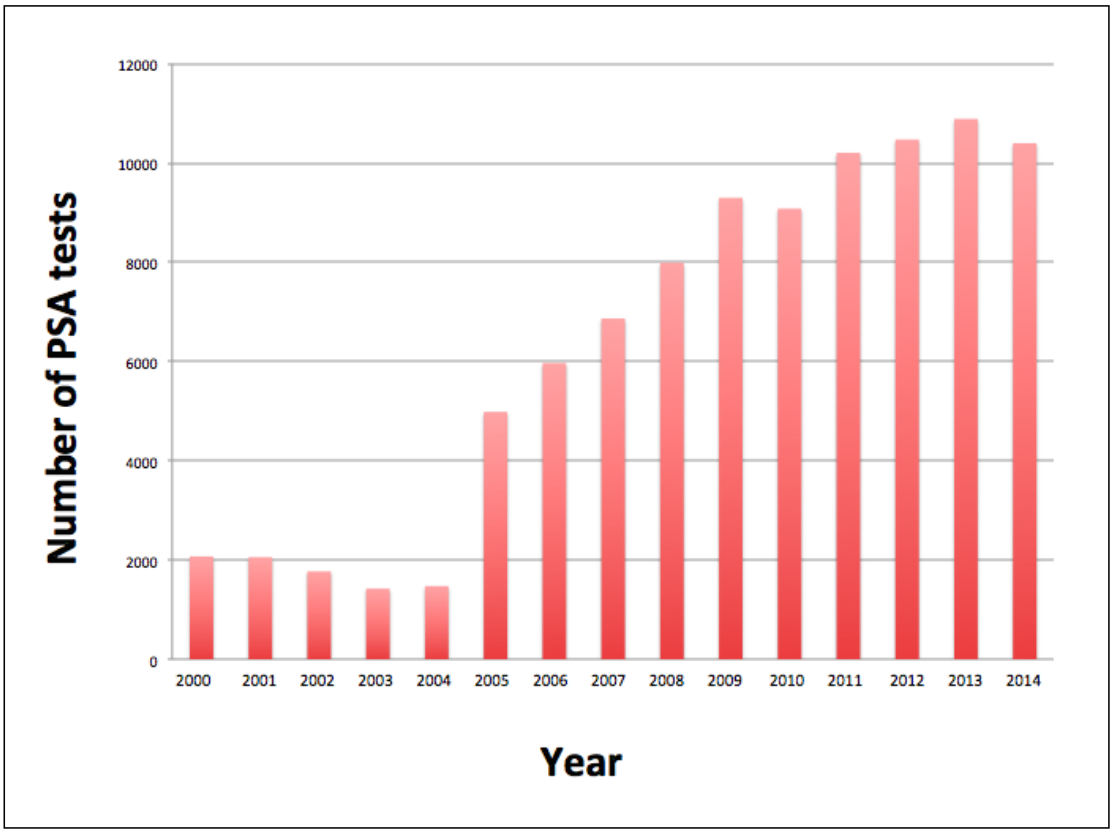


Figure 7: Figure 7. The total number of PSA test at Landspítali University Hospital, Iceland. Since 2005, results from smaller hospitals around the capital were included as well, resulting in a jump in the number of tests between 2004 and 2005.

Contrary to Denmark, curative intended therapy with radical prostatectomy (RP) and radiotherapy (RT) was fully implemented in Iceland around 1990. A two- to three-fold increase in the number of prostate biopsies was observed in Iceland during the period 1983-2003.(121) In 1995, only 12 Danish PC patients underwent RP.(122) Since the study period, i.e. during the last 15 years, curatively intended therapy has been fully implemented in Denmark as well. (123) In 2009, the number of RP operations in Denmark surpassed those done in Iceland: 41 versus 38 per 100,000 inhabitants of Denmark and Iceland, respectively.(122) During this time, the discrepancy of incidence between the 2 countries almost disappeared. The incidence rate in 2011 was 80 per 100,000 World Standard in Denmark compared to 82 per 100,000 World Standard in Iceland.(77)

AIMS AND OUTLINES OF THE THESIS

The overall aim of this study was to explore the clinical setting in neighbouring Nordic countries to explain the differences in survival and excess mortality shown in register-based studies.

In detail, the aims of the project presented in this thesis, which consists of 5 papers (I-V), were three-fold. First, to determine the background for survival differences between Denmark, Iceland, and Sweden. Secondly, to elucidate possible differences in clinical presentation, diagnostics, and survival of patients with clinically localised PC. Thirdly, to validate information reported to the Danish Cancer Registry (DCR) on Danish PC patients diagnosed in 1997.

Paper I:

Register-based studies have shown large survival differences among PC patients in the Nordic countries. The aim of this study was to determine the background of such differences in Denmark, Iceland, and Sweden.

Paper II:

A previous paper showed that relative survival differences of Danish and Icelandic PC patients around 1997 were mostly due to a different proportion of patients with metastases. The study objective was to elucidate possible differences in clinical presentation, diagnostics, and survival of patients with clinically localised PC.

Paper III:

Previous studies in Denmark reported an increase in PC incidence and mortality rates. This study reviewed trends in PC incidence and mortality rates in Denmark during the period from 1943 to 2002.

Paper IV:

In Denmark, cancer incidence figures are available from 1943, and notification of a cancer diagnosis to the Danish Cancer Registry (DCR) has been mandatory since 1987. The aim of this study is to validate information reported to the DCR on Danish PC patients diagnosed in 1997. Thus, the study evaluates the quality of register-based data and whether it is valid for use in international comparisons.

Paper V:

During recent years, new, life-prolonging therapeutic options have been introduced for patients with metastatic PC (M1). The aim of the study was to evaluate survival changes in Danish patients diagnosed in 1997 with a contemporary cohort diagnosed between 2007 and 2013.

METHODS

Study design

The project, on which this Thesis is based, was initially part of the EUROCARE prostate cancer project, which was originally set up in 1989 to assess international differences in cancer survival in Europe. Denmark was included from the start, but Iceland first participated in the EUROCARE-2 project, where PC cases were followed to the end of 1994. The overall aim of the project was to interpret international differences in survival by comparing diagnostic, as well as therapeutic, practices based on collection of clinical data.

Papers I, II, IV, and the historical cohort in Paper V included PC cases identified through population-based cancer registers in Denmark, Iceland, and Sweden. These cases were censored in case of emigration or death during the first 3 months following diagnosis. For Danish and Icelandic cases, an exact date of diagnosis was retrieved from hospital records, and only month and year were available for the time of death. Corresponding dates for Swedish cases were retrieved from the NPCR. All PC patients were followed to the time of death, emigration, or to the end of study (December 31st 2008), whichever came first. Paper III is based entirely on register data. The contemporary cohort in Paper V consisted of an unselected series of men identified in the local pathology database who were diagnosed at the Department of Urology at Frederiksberg Hospital in Denmark during a 7-year period (Jan 1st 2007 to December 31st 2013). They were followed up until death through January 31st 2016. The follow-up for the historical cohort in Paper V was extended to December 31st 2014.

Classification of clinical data

Using a predefined questionnaire (see Appendix 2), tumour (T) stage according to the UICC 2002 TNM classification (35) was retrieved from hospital records for Danish and Icelandic cases and from the NPCR for Swedish patients. A minor simplification of stage T2 was done. Instead of dividing it into T2a, T2b and T2c, it was only divided into 2 subgroups; T2a with unilateral tumour growth (affecting only one lobe) and T2b with bilateral involvement (see page 3 in Guidelines in Appendix 3).

Lymph node involvement (N1) was recorded if lymph node dissection or imaging showed lymph node involvement. N0 patients had no sign of malignancy

following lymph node dissection. Patients were categorized as M1 if they had a positive bone scan and/or positive findings on x-rays of the skeletal system. Other distant metastases were recorded only if they had been verified by histopathology or if diagnostic work-up showed metastasis, using either CT-scan or ultrasonography. If work-up for distant metastases had not been performed, cases were assigned the stage MX. If no assessment of regional lymph node involvement was carried out, cases were assigned the NX stage.

Pre-treatment PSA values were registered as close to the time of diagnosis as possible. Histopathological grade, according to either WHO criteria (26) or Gleason score, (27) was recorded. If both were registered, the Gleason score was used.

In a pre-designed questionnaire (see Appendix 2), we registered the nature of the first contact with the health care system classified as lower urinary tract symptoms, asymptomatic (incidental finding of elevated PSA), or other symptoms (mostly skeletal pain due to bone metastasis, anaemia, or lethargy). Method of diagnosis was classified as: no histological verification (e.g. due to comorbidity or old age), fine-needle aspiration biopsy, Tru-cut biopsy (core biopsy), transurethral resection of prostate (TURP), transvesical prostatectomy (TVP), or bone marrow aspirate.

Treatment with curative intent was recorded for cases undergoing radical prostatectomy, external radiation therapy, or brachytherapy. The date of diagnosis was obtained from hospital records and cancer registries. The date of diagnosis from the hospital records was recorded as the date of histological verification, or, in some cases (those without histological verification), the date of clinical diagnosis based on a high PSA level, imaging results (multiple X-ray or bone scan), and/or abnormal digital rectal exploration of the prostate.

The date of initiation and type of endocrine treatment was recorded. This could include estrogen treatment or different types of androgen deprivation therapy (ADT); androgen receptor inhibitors, bilateral orchiectomy, luteinizing hormone-releasing hormone (LHRH) analogue.

All 3 countries have unique 10-digit civil registration numbers, which allowed us to link the prostate cancer patient to the Civil Registration Systems that contain information on date of death, emigration, and residence of all citizens. Information on time of death was therefore retrieved from the national population registers, making follow-up to death or emigration reliable.

Data collection

Denmark

The Danish cohort consisted of PC cases diagnosed between May 1st and December 31st 1997. The patients lived in 8 of 16 Danish counties, covering approximately 60% of the Danish population. The counties represented 5 urban areas (Copenhagen municipality, Copenhagen county, Frederiksberg municipality, Funen and Aarhus county) and 3 rural areas (Bornholm, North Jutland and West Zealand). Hospital records were retrieved and clinical information was collected using a pre-defined questionnaire (see Appendix 2).

Iceland

The Icelandic cohort was population based, i.e. included all PC cases reported to the ICR being diagnosed from January 1st 1996 to December 31st 1998. Clinical information was collected from hospital records as well as notes from private practice offices of all Icelandic urologists. The same predefined questionnaire was used as in Denmark (see Appendix 2).

Sweden

Swedish cases were only included in Paper I. All PC cases diagnosed in Sweden in 1997 were identified via the Swedish Cancer Register (SCR). The Swedish health care system consists of 6 health care regions, each one possessing a population-based PC register. In 1998, these records were merged into the National Prostate Cancer Register (NPCR). For our study, we accessed data from 2 Swedish regions: the Uppsala-Örebro and Western regions. It covered almost 99% of all new cases in these respective regions in 1997. Ingimarsdóttir and Rusch recoded the data to fit the predesigned questionnaire used in the Danish and Icelandic cohorts, with consultation from Adolfsson and Holmberg.

Denmark, Iceland and Sweden

Patients 90 years and older with PC recorded as their first primary tumour were excluded, as their life expectancy is low. Those in whom PC was detected incidentally at autopsy or only mentioned on a death certificate were excluded. Two Danish cases and one Icelandic case were excluded, as revision of their histological specimens ruled out malignancy.

Patient selection

Paper I

This group was comprised of patients from Denmark, Iceland, and Sweden described under “Data Collection” above.

Paper II

Paper II was restricted to Danish and Icelandic cases with clinically localised prostate cancer (stage T1-2,NX/N0,MX/M0).

Paper III

The paper is based on registry data reported to the DCR. The study population comprised all Danish prostate cancer patients reported to the DCR between 1943 and 2002.

Paper IV

This group was the Danish cohort, described under “Data collection – Denmark”.

Paper V

The historical cohort is a subgroup with metastatic disease of the Danish cohort, described under “Data collection – Denmark”. The contemporary cohort consists of unselective, consecutive series of men diagnosed with metastatic PC at the Department of Urology, Frederiksberg Hospital in Denmark between January 1st 2007 and December 31st 2013.

Statistical methods

In Papers I and II, country-specific incidence and excess mortality rates were compared, with adjustment for prognostic factors.

Paper I

Relative survival was calculated as the ratio between the observed and the expected survival based on population mortality. The observed survival was estimated by the actuarial method, and expected survival was estimated by the Ederer II method.(124) Relative survival is interpretable, as survival from the cancer if no other cause of death is present.

Country-specific population mortality rates were derived from the Human Mortality Database (www.mortality.org). To facilitate comparisons, age standardization was used, with the weights of the International Cancer Survival Standard, as in the Nordic cancer survival study.(125) Relative survival was modelled using additive hazards or excess mortality rates. Follow-up intervals were 0–0.25, 0.25–1, 1–2, 2–3, 3–4 and 4–5 years after diagnosis. However, as excess mortality was nearly constant throughout follow-up, we present excess mortality only for the first 5 years. Two-factor models containing country and one risk factor at a time were fitted. As the M stage appeared to have the greatest effect, analyses were repeated after stratification for M stage.

Relative excess mortality rate ratios (RERs) with 95% confidence intervals (CIs) for Denmark and Iceland relative to Sweden were calculated, as were RERs for risk factor levels, mainly relative to the level with the largest number of patients. The excess mortality risk was modelled in a generalized linear model with a Poisson error structure fitted to collapsed data, using exact survival times. We used SAS macros supplied by Dickman et al.(126) Estimates were made in SAS version 9.2.

Paper II

Chi-square tests were used to test for homogeneity in the distribution of clinical findings between countries; a p-value of less than 0.05 was considered statistically significant. Relative survival was estimated as described in Paper I. Age-standardization used was according to the International Cancer Survival Standard as described in the Nordic Cancer Survival Study.(125) Expected survival was estimated using national population mortality among men by one-year age and calendar periods using the Ederer II method.(125)

Paper III

Between 1943 and 1977, the DCR coded newly diagnosed PC patients based on a modified version of the ICD-7. From 1978 onwards the ICD-O was used with simultaneous conversion of the coding to match the ICD-7.(127) The cohort of this paper consists of an extraction from the DCR for the period 1943-2002. Because the data was not linked with records from the Danish Register of Causes of Death, preliminary numbers available from the DCR at the time of the study for the period 2000 to 2002 were used. Data on PC cases based solely on information from death certificates were therefore not included for the last 3 years in the last 5-year interval presented. Thus, the number of newly diagnosed cases in the last 5-year period is underestimated by approximately 40 cases per year according to The National Board of Health and Welfare in Denmark (Sundhedsstyrelsen).(128)

The data extracted from the DCR and used in this paper were the date of diagnosis and clinical stage. The DCR coded stage into 4 different groups; localised, regional spread, metastatic or unknown. Data from The Danish Register of Causes of Death were used to calculate mortality rates. PC was first classified as a cause of death in the DCR from 1953. Since the cause of death was not available (at the time of the study) from the time period 2001 and 2002, the mortality rate between 1998 and 2002 could not be calculated.

Age-standardized incidence and mortality rates were calculated based on the World Standard Population and divided into 5-year periods. Incidence rates were divided into 5-year periods for patients older than 50 years of age. The data was further stratified into cases younger than 70 years old, or 70 years old and older. Data on population size was obtained from Statistics Denmark (Danmarks Statistik). The trends in incidence and mortality rates were tested by means of linear regression. Trends in clinical staging were assessed by the Chi-test for trend.(129) A p-value of less than 0.05 was considered statistically significant.

Paper IV

The reported date of diagnosis, clinical stage, and primary treatment was compared to data retrieved from medical records. Information on the date of diagnosis (recorded as month and year of the patient´s first contact with the health care system), clinical stage (categorized as localised, regional, metastatic, or unknown), and treatment within the first 4 months were retrieved from the DCR. Treatment data on surgical intervention was categorized as diagnostic, palliative, or radically attempted procedures. Other types of treatment recorded were radiation, chemotherapy, androgen deprivation therapy (ADT), no treatment, and treatment unknown or unstated.

In 1997, the DCR coded stage into 4 different groups (localised, regional, metastatic, and unknown) as indicated on the notification form by the clinician. Cross-tables based on T- and M-stages were used to validate tumour stage; T1-2 represented localised, T3 regional or locally advanced, and T4 with involvement of a structure within the pelvic region. N-stage was registered for a few cases. This information was not considered consistent and hence not taken into account in this study. All patients were reported to have localised PC and survival was stratified according to M-stage.

The time interval between the reported and the observed date of diagnosis was measured in months. Survival analysis was computed by means of the PROC LIFETEST procedure in SAS, which computes nonparametric tests to compare the survival curves of 2 or more groups.

Paper V

Differences in baseline characteristics between the cohorts were tested using the Chi-squared-test for categorical variables and the Mann–Whitney U test for continuous variables. Kaplan-Meier survival analysis was used to estimate overall survival, and log-rank analysis was used to compare survival between the 2 cohorts. Cumulative incidences of PC-specific death and other causes of mortality were analysed using the Aalen–Johansen method for competing risks. Non-PC death was treated as a competing event when analysing risk of PC death and vice versa. Gray's test was used to assess differences in the cumulative incidence between the cohorts. Cox regression analyses was used to estimate the risk of death for men with complete baseline information and included age (continuous), PSA (continuous), CCI (0, 1, ≥2), clinical T-stage (T1, T2, T3 and T4), and primary treatments (GnRH agonists, orchiectomy, total androgen blockade, androgen receptor inhibitors, oestrogens). Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Both univariate and multivariate Cox regression analyses included only men with complete baseline information in terms of age, PSA, CCI, clinical T category, and first-line treatment.

The 1-, 3- and 5-year relative survival was calculated. Follow-up for death was updated until December 31st 2014 and January 31st 2016 for the historical cohort and the contemporary cohort, respectively. Observed survival was estimated using the actuarial method and expected survival by the Ederer II method. Expected survival was estimated from male population mortality rates stratified by age and calendar time in one-year intervals. Since the age distribution of patients differs over time, 1-, 3- and 5-year relative survival figures were age-standardised with the International Cancer Survival Standard as used in the

Nordic Cancer Survival Study. For the contemporary cohort, not all patients could be followed for death up to 5 years and hence were censored accordingly.

All tests were two-sided, and the significance level was set to $p<0.05$. Statistical analysis was performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Chapter 2: Differences in survival from PC in Denmark, Iceland and Sweden.

RESULTS

Paper I – Differences in survival from prostate cancer in Denmark, Iceland, and Sweden

In total, 3176 patients in Denmark, Iceland and Sweden under the age of 90 years with newly diagnosed PC were included in the study. Table 2 shows the numbers of cases and the criteria for exclusion before analysis.

Distribution of inclusion and exclusion criteria	DK	IS	SWE
Prostate cancers in cohorts from cancer registers or regional clinical databases	675	438	2566
Exclusions based on register information			
Prostate cancer diagnosis not confirmed by pathology report	-	-	17
Incidental finding at autopsy or death certificate only	18	12	65
Previous or simultaneous other cancer diagnosis	72	38	165
Not in database at time of registration	10	-	-
Hospital records read	575	388	2319
Exclusions based on hospital records/not in National Prostate Cancer Register (Sweden)			
Previously diagnosed	4	-	2
Diagnosis altered after pathological revision	2	1	-
Incidental finding at autopsy	1	-	-
Previous or simultaneous other cancer diagnosis	-	2	-
Not found in hospital record/National Prostate Cancer Register	3	-	26
Patients eligible, all ages	565	385	2291
Patients included (age < 90 years)	549	374	2253
DK, Denmark; IS, Iceland; SWE, Sweden.			

Table 2: Inclusion and exclusion criteria in the study cohorts of patients with prostate cancer diagnosed in and around 1997 in Denmark, Iceland, and Sweden.

Table 3 shows the relative survival in the 3 cohorts and in the population-based Nordic Cancer Study.(102) The Icelandic cohort was population-based, so it was known beforehand that the RS calculations would be equal to those based on the ICR. Even though the Danish and Swedish cohorts were not population-based, their RS was shown to be representative of the whole PC population in each of the 2 countries.

Study	No. of patients	5-Year RS (CI)	10-Year RS (CI)
Denmark			
Study cohort	565	43 (38-49)	24 (19-30)
CRG	7616	42 (40-45)	22 (21-24)
Iceland			
Study cohort	385	75 (67-84)	65 (56-75)
CRG	709	76 (71-82)	63 (57-68)
Sweden			
Study cohort	2291	72 (66-78)	52 (47-58)
CRG	29116	72 (71-74)	52 (51-53)

Table 3: Age-standardized relative survival (RS) and with 95% confidence interval (CI) in the different cohorts of prostate cancer patients in Denmark, Iceland, and Sweden around 1997 and in the national cancer registers (CRG) from the Nordic Survival Study, 1994-1998.

Table 4 summarizes clinical information by country. For each factor, a test for homogeneity in distribution between countries is presented, which shows significant differences in the distribution of the factors studied. Further, it shows the relative prognostic impact of each level of the factors in further analyses adjusted for country. No significant systematic correlations were found between age and various clinical parameters.

The proportion of Danish patients with metastases at diagnosis was more than twice that of Iceland and Sweden. Lymph node staging had been performed in only a limited number of cases. Significant differences between countries in clinical T stage and PSA level were found, with Danish patients having, on average, higher T stage and PSA levels. The histological classification system used differed between countries: Both WHO grade and Gleason score were

recorded for about 50% of patients in Sweden, mainly WHO grade was recorded for Danish patients, and predominantly Gleason scores for Icelandic patients.

Danish patients had statistically significantly more often tumours that were poorly differentiated. Attempts to transform WHO grade to Gleason score in the Swedish data were futile. Therapy with curative intent was used significantly more frequently in Iceland and Sweden than in Denmark (Table 4).

The relative prognostic effect of clinical factors and treatment within the first 6 months of diagnosis was determined by analysing the 5-year relative excess mortality rates for each factor, adjusted for country. Age at diagnosis had only a minor effect. M1 disease increased the RER ten-fold relative to M0. Increasing tumour burden, either as higher T stage or PSA level, increased the risk.

The RER increased with increasing Gleason scores in Iceland and Sweden, while in Denmark and Sweden the RER increased with less differentiated tumours in the WHO grade. Hormonal therapy within the first 6 months was associated with a nearly six-fold increase in RER. Therapy with curative intent was associated with a reduced risk RER = 0.01 (CI 0.00-16.4).

Figure 8 shows the 5-year excess mortality rate ratio for Danish and Icelandic patients relative to Swedish patients overall and adjusted for several pre-diagnostic characteristics, i.e., age, clinical T stage, M stage, PSA level at diagnosis, and whether treatment was given within 6 months with either hormones or curative intent therapy. These survival rates are shown for all patients and stratified by M status. In a comparison of Icelandic and Swedish patients, none of the factors had a significant effect.

Overall, significantly greater relative excess mortality was found for Danish compared to Swedish patients with RER = 2.46 (CI 2.02-3.00), but not for Icelandic patients (RER = 0.90, CI 0.65-1.25). Adjusting for M status among Danish patients gave the largest decrease (RER = 1.44, CI 1.18-1.75), and adjusting for PSA level resulted in a slightly higher RER (1.54, CI 1.24-1.90). Adjustment for clinical T stage or curative intended therapy had no significant effect. Hardly any effect was seen after adjusting for ADT or age. In a comparison of Icelandic and Swedish patients, none of the factors had a significant effect. Stratification by M status reduced the ratio between the Danish and the Swedish excess rates to 1.31 (CI 1.05-1.62) for the M1 strata and 1.39 (CI 0.56-3.47) for the M0 strata. Additional adjustment for other factors had only minor effects. In the comparison of Iceland and Sweden, only small, non-significant effects were seen after stratification by M status.

Patient factor	DK (n=549) (%)	IS (n=374) (%)	SWE (n=2253) (%)	Test for homogeneity (*p*)	RER (95% CI)	Test for effect of factor (*p*)
Age at diagnosis (years)				0.005		0.00988
40-59	5	5	6		0.93 (0.67,1.29)	
60-69	21	30	24		0.77 (0.62,1.57)	
70-79	45	45	46		1.00	
80-89	29	20	25		1.23	
Clinical T stage				≤ 0.0001		≤ 0.0001
T0-1	16	29	22		0.41 (0.24,0.71)	
T2	40	47	31		1.00	
T3	22	18	36		2.42 (1.90,3.08)	
T4	11	5	8		4.49 (3.41,5.91)	
TX	11	1	2		2.45 (1.65,3.65)	
N stage				≤ 0.0001		
N0	2	5	13			
N1	4	7	2			
NX	94	89	84			
M stage				≤ 0.0001		≤ 0.0001
M0	23	56	40		1.00	
M1	43	20	19		10.3 (7.49,14.2)	
MX	34	24	41		2.06 (1.43,2.97)	
PSA (ng/ml) at diagnosis				≤ 0.0001		≤ 0.0001
0-3.9	3	9	5		0.29 (0.07,1.18)	
4-9.9	5	19	15		0.22 (0.07,0.67)	
10-99.9	38	51	53		1.00	
≥ 100	39	17	23		4.34 (3.50,5.37)	
Unknown/not reported	15	5	4			
Gleason score				≤ 0.0001		≤ 0.0001[a]
2-5	6	42	19		0.03 (0.01,0.19)	
6-7	9	35	20		0.27 (0.19,0.39)	
8-10	13	16	11		1.00	
Unknown/not reported	72	8	51			
WHO grade				≤ 0.0001		≤ 0.0001[b]
Well differentiated	15	2	28		0.38 (0.23,0.62)	
Moderately differentiated	21	1	41		1.00	
Poorly differentiated	25	1	25		2.70 (2.15,3.39)	
Unknown/not reported	40	97	6			
Hormone treatment < 6 months				0.002		≤ 0.0001
Yes	45	44	52		5.89 (4.43,7.82)	
No	55	56	48		1.00	
Treatment with curative intent				≤ 0.0001		≤ 0.0001
Yes	2	18	13		0.01 (0.00,16.4)	
No	98	82	87		1.00	

PSA, prostate-specific antigen; WHO, World Health Organization; IS, Iceland; DK, Denmark; SWE, Sweden.
[a] Only Iceland and Sweden.
[b] Only Denmark and Sweden.

Table 4: Patient characteristics in a prostate cancer cohort study around 1997 in Denmark, Iceland, and Sweden and the relative impact of prognostic patient factors estimated as relative excess mortality rate ratios (RERs) adjusted for country.

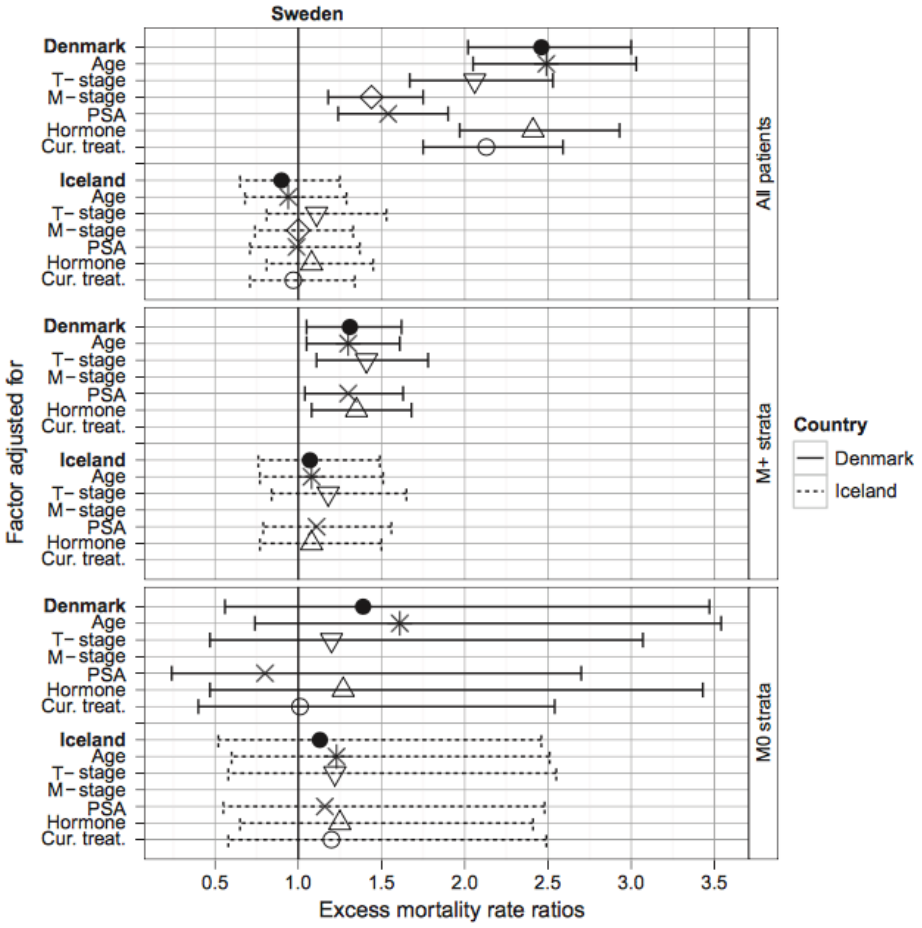


Figure 8: Five-year relative excess mortality rate ratios (RERs) for prostate cancer in 1997 in Denmark and Iceland, relative to Sweden, overall and adjusted for each pre-diagnostic characteristic or treatment factor for all patients and stratified by metastatic status (M1 and M0).

PSA at diagnosis (ng/ml)	DK (n=187) (%)	IS (n=91) (%)	SWE (n=931) (%)	Test for homogeneity (*p*)	RER (95% CI)	Test for effect of factor (*p*)
< 50	38	71	67	≤ 0.0001	1.00	≤ 0.0001
≥ 50	35	14	27		7.33 (3.79,14.18)	
Unknown	27	14	6		5.19 (2.37,11.35)	

DK, Denmark; IS, Iceland; SWE, Sweden; RER, relative excess mortality rate; PSA, prostate-specific antigen.

Table 5:Distribution of prostate-specific antigen (PSA) level and relative excess mortality rate ratios (RERs) among patients with unknown metastatic level in a prostate cancer cohort study, 1997, in Denmark, Iceland, and Sweden and relative prognostic impact of PSA level (RER) adjusted for country.

Danish patients who were not evaluated for metastatic disease had significantly higher PSA levels or an unknown PSA value compared to the Icelandic and Swedish patients. The RERs for patients with unknown M status with PSA equal or higher than 50 ng/ml or unknown were 7.33 (CI 3.79-14.2) and 5.19 (CI 2.37-11.4), respectively, relative to those with PSA level less than 50 ng/ml (Table 5).

Cohort	Metastatic status M0	M1	Unknown
Denmark, 1997, 8/16 counties	12.3	22.0	17.1
Iceland, 1996-1998	62.9	23.3	26.6
Sweden, 1997			
Uppsala-Örebro region	47.3	21.2	46.4
Western (Västra) region	44.6	18.6	34.3

Table 6: Age-standardised incidence rates per 100,000 by metastatic status in 4 different prostate cancer cohorts around the year 1997.

The age-standardised incidence rates in the 4 cohorts stratified by M status are shown in Table 6. No difference was found in the rates of metastatic PC among the cohorts. The rates for M0 PC were highest in Iceland, followed by both Swedish regions, while Sweden had the highest rates of unknown metastatic status.

Paper II – Localised prostate cancer in Denmark and Iceland

The study-population consisted of 443 patients with clinically localised (T1-2, N0/NX and M0/MX) prostate cancer, Table 7.

Distribution of inclusion and exclusion criteria	DK	IS
Prostate cancers in original cohort	675	438
Exclusions based on register information		
Incidental finding at autopsy or death certificate only	18	12
Previous or simultaneous diagnosis of another type of cancer	72	38
Not registered at time of cohort definition	10	-
Hospital records studied	**575**	**388**
Exclusions based on hospital records/clinical register		
Hospital diagnosis more than two years before diagnosis in CR	4	-
Diagnosis altered after pathological revision	2	1
Incidental finding at autopsy	1	-
Previous or simultaneous diagnosis of another type of cancer	-	2
No hospital records	3	-
Age 90 and above	16	11
Stage M1	234	75
Stage N1	4	17
Stage T3 or T4	71	43
Missing T-stage and TX	34	2
Patients included in the study	**206**	**237**
DK, Denmark; IS, Iceland; CR, cancer registry.		

Table 7: Inclusion and exclusion criteria for 2 cohorts of patients with localised prostate cancer (T1-2,N0/X and M0/X) in Denmark and Iceland.

Baseline characteristics are shown in Table 8. The mean age at diagnosis of PC was significantly higher in Denmark. LUTS were predominant in both populations. The percentage of Icelandic patients diagnosed following an incidental PSA test was five-fold higher than in Denmark. Most Danish patients (63%) were diagnosed following TURP, while a similar proportion of Icelandic patients (61%) were diagnosed by means of Tru-cut biopsies. Significantly more Icelandic patients had clinical stage T1c, whereas the proportion of patients with T2 disease was significantly higher in Denmark.

Danish patients had higher PSA values (statistically significant), and a higher proportion had no pre-diagnostic PSA value. The proportion of patients with a PSA level above 100 ng/ml was more than twice as high in Denmark (16%) as in Iceland (7%). The majority of Danish patients had a tumour graded by the WHO grading system. The largest group of Danish cases had well differentiated tumour (30%), while 19% had moderate and 16% poorly differentiated tumour. Almost all Icelandic cases had a tumour graded by the Gleason score; most had well differentiated tumours, reflected by the fact that 58% had a low Gleason score (≤ 5); 30% had moderately differentiated tumours (Gleason score 6-7), and only 8% had poorly differentiated tumours (Gleason score ≥ 8).

Diagnosis without histological verification was more common in Denmark. This subgroup in Denmark was significantly older than the rest of the Danish cohort (data not shown). In both countries, lymph node staging was rarely performed. Work-up for distant metastases was carried out significantly more often in Iceland (Table 8).

The percentage of patients receiving curatively intended therapy was significantly higher in Iceland. Endocrine therapy was introduced earlier in Iceland, but at the end of the follow-up period, a larger proportion of Danish patients (58% in Denmark vs. 44% in Iceland) had been treated with endocrine therapy (Table 8).

Overall survival of men diagnosed with PC in Iceland was significantly higher than that of their Danish counterparts. At the end of follow-up, 54% of Icelandic men and 25% of Danish men were alive (not shown). Figure 9 shows the cumulated relative survival in the 2 countries ($p<0.001$ at 10 years after diagnosis).

The data were stratified according to metastatic work-up, i.e. for M0 and MX patients. Metastatic work-up was performed significantly more frequently in Iceland (65%) as compared to Denmark (41%). Patients with localised T1-T2 PC who underwent metastatic work-up had a tendency towards being younger than those with stage MX. No significant age difference between the 2 countries was found for M0 patients (Table 8). There were no differences in pre-treatment PSA present for M0 patients (Table 8), while significant differences remained among those with MX disease (Table 9).

Characteristics of the study cohort	DK all (n=206) %	IS all (n=237) %	p value*	DK M0 (n=85) %	IS M0 (n=153) %	p value*
Age, mean (sd)	74.7 (7.6)	72.7 (8)	0.001	72.9 (7.7)	71.1 (7.9)	0.089
Nature of first contact			<0.001			0.023
LUTS	173 (84)	187 (79)		72 (84.7)	114 (74.5)	
Incidental PSA testing	5 (2.4)	29 (12)		2 (2.4)	20 (13.1)	
Symptoms other than LUTS	28 (13.6)	21 (8.9)		11 (12.9)	19 (12.4)	
Mode of detection						< 0.001
No histology	22 (10.7)	3 (1.3)	<0.001	8 (9.4)	1 (0.7)	
Fine needle aspiration (FNA)	1 (0.5)	1 (0.4)		0 (0)	1 (0.7)	
Needle-biopsy (Tru-cut)	54 (26.2)	144 (61)		34 (40)	111 (72.6)	
TURP or TVP	129 (62.7)	89 (38)		43 (50.6)	40 (26.1)	
Clinical stage			< 0.001			0.005
T1a or T1b	66 (31)	63 (27)		26 (30.6)	23 (15)	
T1c	7 (4.4)	37 (16)		5 (5.9)	23 (15)	
T2	133 (64.6)	137 (58)		54 (63.5)	107 (69.9)	
Pretreatment PSA value (ng/ml)			< 0.001			0.225
Normal (0-3.9)	15 (7.3)	30 (13)		9 (10.6)	11 (7.2)	
4-9.9	23 (11.2)	60 (25)		14 (16.5)	40 /26.1)	
10-99.9	104 (50.5)	116 (49)		45 (52.9)	88 (57.5)	
≥ 100	33 (16)	17 (7.2)		10 (11.8)	11 (7.2)	
Result unknown or not performed	31 (15)	14 (5.9)		7 (8.3)	3 (2)	
Histological grading						
Gleason score						
Gleason score 2-5	18 (8.7)	137 (58)		4 (4.7)	78 (51)	
Gleason score 6-7	23 (11.2)	70 (30)		6 (7.1)	52 (34)	
Gleason score 8-10	20 (9.7)	18 (7.6)		7 (8.2)	16 (10.5)	
Unknown	145 (70.4)	12 (5.1)		68 (80)	7 (4.6)	
WHO-criteria						
Well differentiated	61 (29.6)	7 (3)		30 (35.3)	5 (3.3)	
Moderately differentiated	39 (18.9)	1 (0.4)		18 (21.2)	1 (0.7)	
Poor differentiated	31 (15.1)	0 (0)		13 (15.3)	0 (0)	
Unknown	75 (36.4)	229 (97)		24 (28.2)	147 (96.1)	
N stage			0.104			0.227
N0	5 (2.4)	13 (5.5)		4 (4.7)	13 (8.5)	
NX	201 (97.6)	224 (95)		81 (95.3)	140 (91.5)	
M stage			< 0.001			
M0	85 (41.3)	153 (65)				
MX	121 (58.8)	84 (35)				
Curative intended therapy						
Radical prostatectomy	5 (2.4)	39 (17)		4 (4.7)	37 (24.2)	
Curative radiotherapy	1 (0.5)	14 (5.9)		0 (0)	14 (9.2)	
No curative treatment	200 (97.1)	184 (78)		81 (95.3)	102 (66.7)	
Endocrine therapy			< 0.001			0.001
Within 3 months of diagnosis	31 (15.1)	57 (24)		15 (17.7)	40 (26.1)	
More than 3 months after diagnosis	89 (43.2)	48 (20)		40 (47.1)	37 (24.2)	
No hormonal treatment	86 (41.8)	132 (56)		30 (35.3)	76 (49.7)	
TURP after diagnosis	61 (29.6)	36 (15)	< 0.001	35 (41.2)	23 (15)	< 0.001

* Chi-square tests have been performed for all categorical variables and t-test for age.
PSA, prostate-specific antigen; WHO, Worlds Health Organization; DK, Denmark; IS, Iceland.

Table 8: Baseline characteristics of 443 men diagnosed with localised prostate cancer in and around 1997 in 8 of 16 counties in Denmark and all of Iceland.

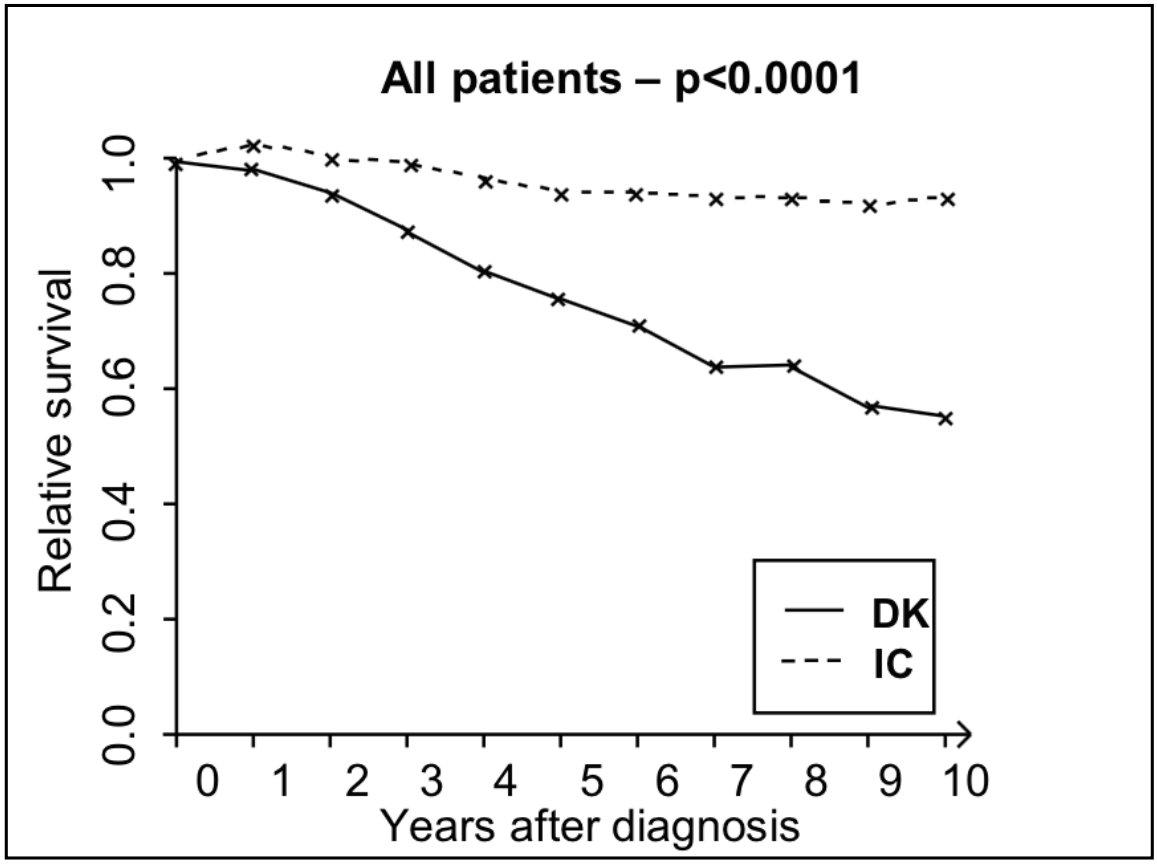


Figure 9: Relative survival of men diagnosed with prostate cancer around the year 1997 in Denmark (DK) and Iceland (IC) during ten years of follow-up.

PSA (ng/ml)	Denmark MX (%)	Iceland MX (%)	p value*
0-3.9	6 (5.0)	19 (22.6)	< 0.001
4-9.9	9 (7.4)	20 (23.8)	
10-99.9	59 (48.8)	28 (33.3)	
≥ 100	23 (19.0)	6 (7.1)	
Unknown	24 (19.8)	11 (13.1)	

* Chi-square tests have been performed for categorical variables.
PSA, prostate-specific antigen.

Table 9: Pre-treatment PSA levels for Danish and Icelandic prostate cancer patients diagnosed with MX disease diagnosed in and around 1997.

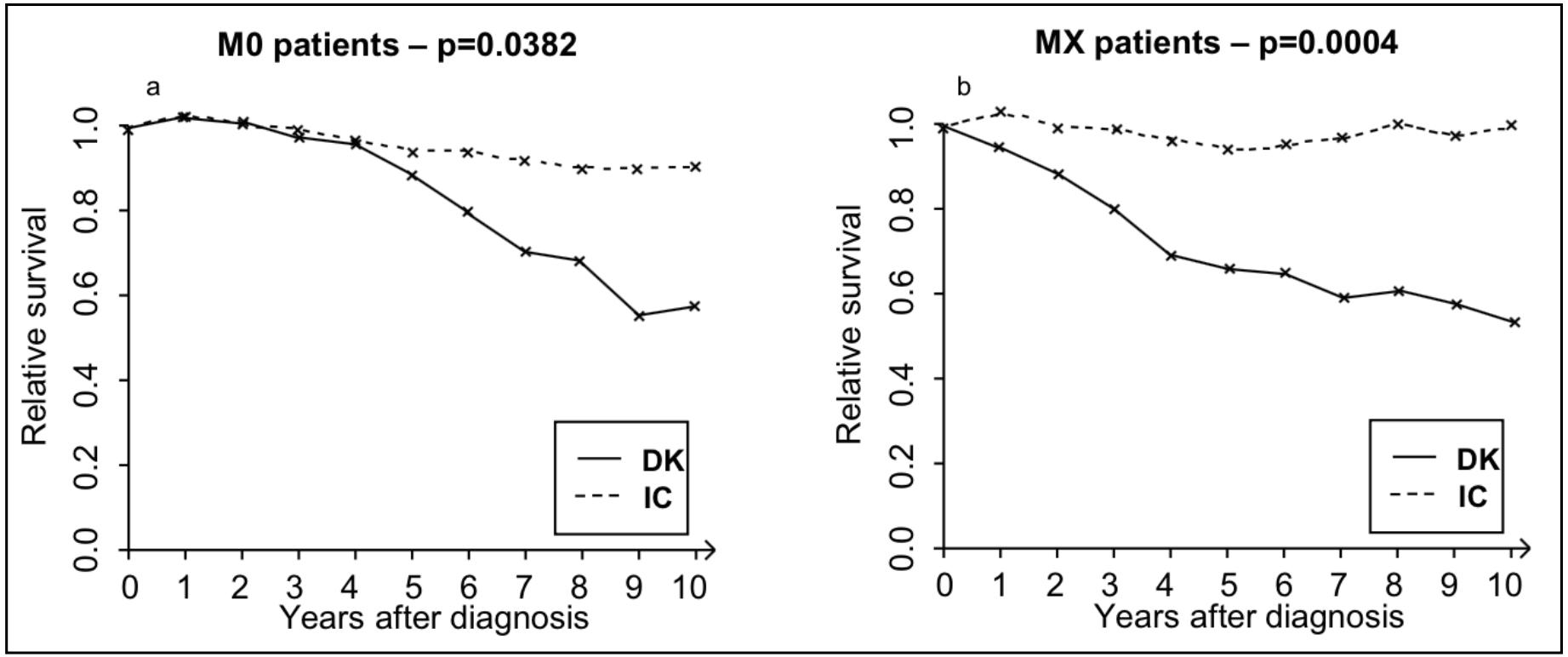


Figure 10: Relative survival for Danish (DK) and Icelandic (IC) patients diagnosed around the year 1997 among M0 patients (10a) and MX patients (10b).

A similar pattern in mode of detection and nature of first contact for all patients prevailed for the M0 group. In both countries, endocrine therapy was used less commonly among the men diagnosed with M0. No significant difference in relative survival was observed between the Icelandic and Danish men diagnosed with M0 disease during the first 4 years of follow-up. After 5 years, relative survival for Icelandic M0 patients was fairly constant but decreased sharply in Denmark (Figure 10a). The 10-year relative survival for men in Iceland diagnosed with MX disease was significantly higher compared to their Danish counterparts (Figure 10b).

Paper III – Prostate cancer trends in Denmark, 1943 to 2002

Between 1943 and 2002, a total of 60,654 cases of PC were reported to the DCR. The number of cases increased from 1310 cases during the first 5-year period to 9242 cases between 1998 and 2002. The trends in age-standardized incidence and mortality rates in Denmark are shown in Figure 11.

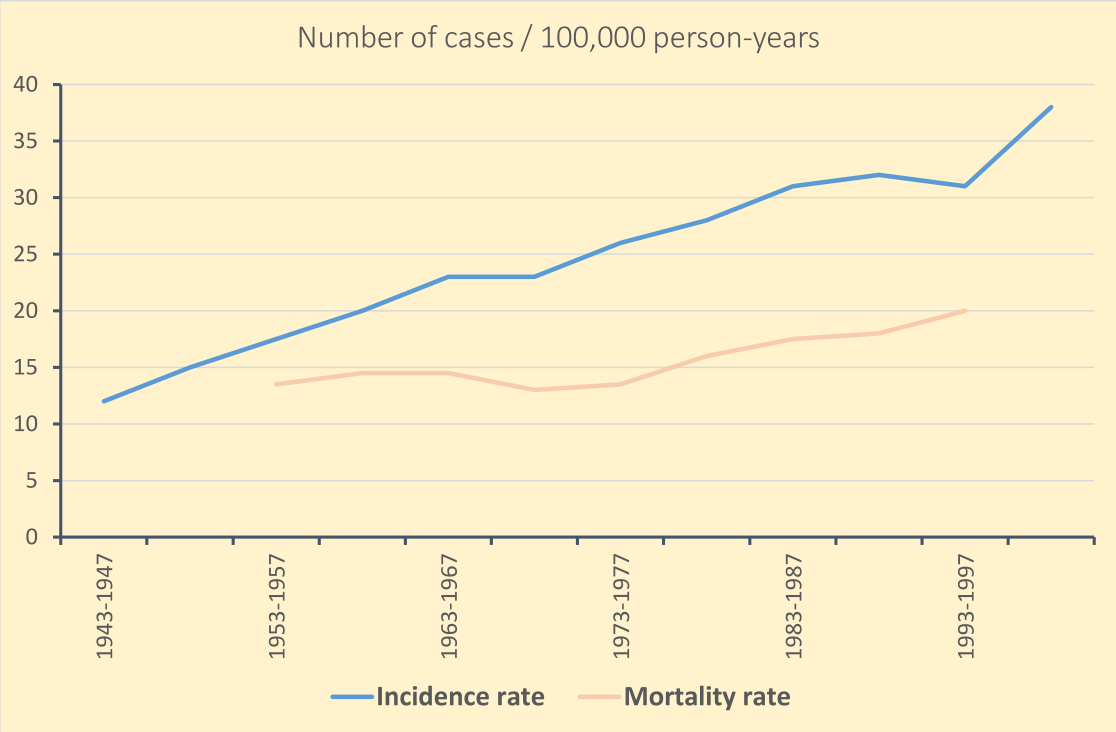


Figure 11: Age-standardized (World Standard Population) incidence and mortality rate in Denmark from 1943 to 1997. Cases per 100,000 person-years.

During the observational period, the incidence of PC rose from 11.4 per 100,000 from 1943-1947 to 38.2 per 100,000 from 1998-2002, (r^2 = 0,97, p<0,05). The mortality rate increased from 14 per 100,000 in the beginning of the 1950s to 19 per 100,000 from 1993-1997, (r^2 = 0,84, p<0,05). During the study period, a significant tendency towards a rising average age at diagnosis was observed, i.e. from 70.2 years in 1943-1947 to 74.2 years in the period 1993-1997. However, during the latest (at the time of the study) available 5-year period, between 1998-2002, the average age at diagnosis had fallen to 73 years. For all age groups (divided into 5-year age groups), an increasing incidence of PC was observed, although with a less obvious rise in the oldest age groups during the last 5-year periods analysed in the study.

The development of age-standardized incidence stratified to the reported stage in the period 1943 to 2002 is shown in Figure 12.

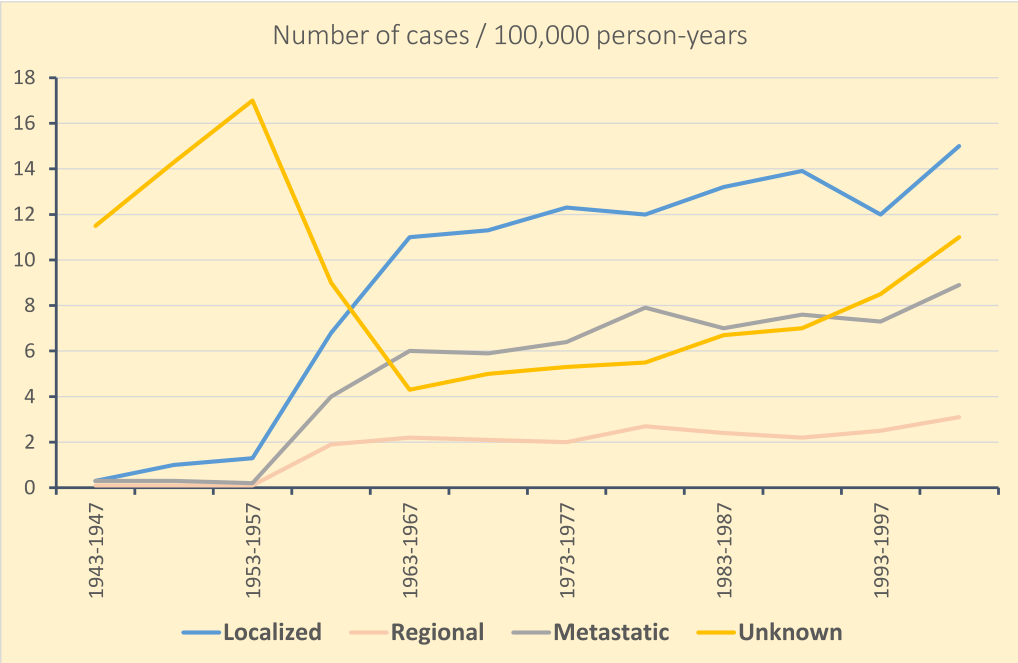


Figure 12: Trends in prostate cancer incidence by stage during the period 1943 to 2002 with cases per 100,000 person-years (age-standardized, World Standard Population).

The reported data on staging during the early years were inaccurate, as most cases were reported with an unknown disease stage at diagnosis. From the 5-year period between 1963-1967, a significant rise in incidence for all stages was observed. Henceforward, the percentage of cases reported with localised prostate cancer fell significantly and simultaneously a rise in the proportion of cases with unknown stage at diagnosis was observed.

Since a special focus had been put on younger patients to identify possible candidates for curative therapy, the development in age-specific incidence for cases below 70 years of age was especially of interest. Figure 13 shows the trend in age-specific incidence for cases under the age of 70 years and 70 years or older, respectfully. A considerable rise in incidence of prostate cancer was observed among younger patients.

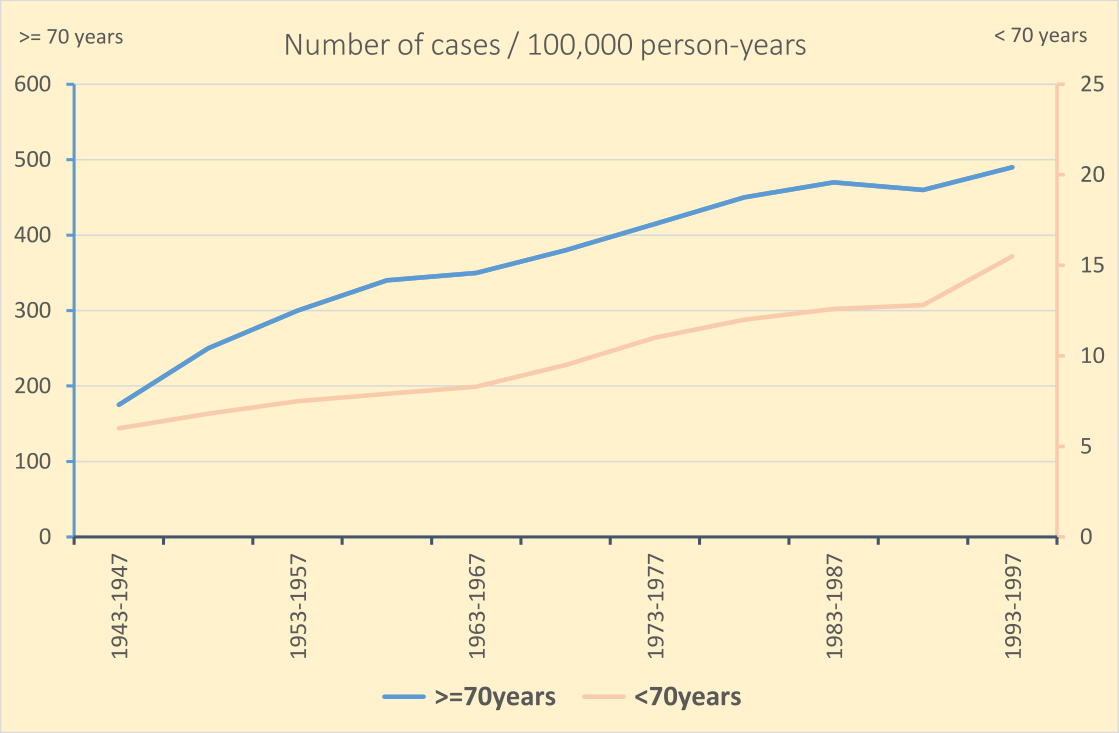


Figure 13:Trends in age-specific prostate cancer incidence in Denmark for cases under 70 years of age and those 70 years and older.

Table 10 shows the number of newly diagnosed PC cases during the last two 5-year periods available at the time of the study. The rising incidence of PC among patients younger than 70 years was predominantly due to a rise in the number of cases of clinically localised PC.

Stage	Localized n (%)	Regional n (%)	Metastatic n (%)	Unknown n (%)	Total
1993-1997					
Age, years					
< 70	729 (35)	167 (8)	664 (32)	520 (25)	2080
≥ 70	2022 (38)	317 (6)	1491 (28)	1508 (28)	5338
1998-2002					
Age, years					
< 70	1400 (44)	334 (10)	747 (23)	700 (22)	3181
≥ 70	2026 (33)	362 (6)	1700 (28)	1973 (33)	6061

Table 10: Exact numbers and percentage distribution of stage of newly diagnosed prostate cancer in Denmark during the periods 1993-1997 and 1998-2002, among patients younger than 70 years of age and those 70 years of age and older.

Paper IV – Quality assessment of the DCR

Between May 1st and December 31st 1997, a total of 575 patients, living in 8 Danish counties, were diagnosed with PC as their first primary cancer and reported to the DCR. Hospital records could not be retrieved for 3 patients; one was only mentioned on a death certificate, and, following pathological revision, 2 patients were found not to have PC (Table 11). Thus, 569 patients were included in the study. The mean age at diagnosis was 74.6 years (s.d. 8.6 years).

Distribution of inclusion and exclusion criteria	
Prostate cancers in cohort from the DCR database	675
Exclusions based on DCR data	
Incidental finding at autopsy or death certificate only	18
Previous or simultaneous other cancer diagnosis	72
Not in database at time of registration	10
Hospital records obtained	575
Exclusions based on hospital records	
Diagnosis altered after pathological revision	2
Incidental finding at autopsy	1
Previous or simultaneous other cancer diagnosis	3
Patients included	569

Table 11: Inclusion and exclusion criteria in a population-based study cohort of patients with prostate cancer diagnosed between May 1st and December 31st 1997, in 8 counties in Denmark

Of these, 494 patients (87%) had histologically verified prostate cancer, and in the remaining 75 patients (13%), diagnosis was based on clinical findings. Distribution of TNM-stages, pre-treatment PSA-values from hospital records, and stage registration from the DCR are shown in Table 12.

The hospital date of diagnosis was generally the date when diagnosis was histologically verified, while the DCR date applied the date of first contact with the health care system. For 70% of cases, there was no difference between the 2 dates, and overall, 543 (95%) of the patients had a difference of less than 3 months. Only ten patients had a difference exceeding one year (Table 13). Correction of dates of diagnosis had no impact on survival (data not shown),

Baseline characteristics	No. of patients N = 569	Percent (%)
T stage		
T1	87	15
T2	232	41
T3	122	21
T4	60	11
TX	68	12
N stage		
N0	10	2
N1	25	4
NX	534	94
M stage		
M0	129	23
M1	242	43
MX	198	35
Pretreatment PSA value (ng/ml)		
0-3.9	19	3
4-9.9	27	5
10-49.9	129	23
50-99.9	82	14
≥ 100	224	39
Not performed, unknown	88	15
Stage, DCR		
Localized	186	33
Regional	43	8
Metastatic	166	29
Unknown	174	31

Table 12: Distribution of clinical stage and PSA levels at diagnosis from hospital records, and the stage reported to the DCR of Danish prostate cancer patients diagnosed between May 1st and December 31st 1997, in 8 counties in Denmark.

Difference in dates	Hospital date before DCR date	DCR date before hospital date	Total
0 months	0	0	400
1-3 months	36	107	143
4-12 months	12	4	16
> 1 year	7	3	10
Total	55	114	569

Table 13: Time difference between the reported date of diagnosis to the DCR and the date of diagnosis found in hospital records for Danish prostate cancer patients diagnosed between May 1st and December 31st 1997, in 8 counties in Denmark.

Thirty-three patients were reported to the DCR as having undergone radical prostatectomy (RP). Two of these cases were confirmed in the hospital records, while 24 of the 33 patients were treated with transurethral resection of the prostate (TURP) within 4 months following diagnosis. According to hospital records, 5 additional patients underwent curative surgery within the first 4 months following diagnosis without being reported to the DCR. Curative radiotherapy (RT) was reported to the DCR in 16 cases, but based on hospital records, only 4 patients had curative intended radiation therapy, and only one was registered with RT in both sources (Table 14).

Hospital records identified 86 patients with T1-2 disease without distant metastases (M0), but only 56 of these patients (65%) were reported to the DCR as having localised disease (Table 15). According to hospital records a total of 242 patients were confirmed having distant metastases (M1) at diagnosis, irrespective of their T-stage, but only 139 of these cases (57%) were reported to the DCR as such (Table 14 and Table 15). Hence, 103 cases were found to have distant metastases according to hospital records, but were not reported to the DCR (Table 14). Lymph-node staging was only rarely performed, and had to be left out in validating the quality due to limited cases

	Hospital records	%	DCR	%	Matching cases*	%
M1	242	43	166	29	139	57
Radical prostatectomy (RP)						
Yes	7	1	33	6	2	29
No	541	95	536	91	507	94
Unknown	21	4	21	4	0	0
Radiation therapy (RT)						
Yes	4	1	16	3	1	25
No	544	95	553	93	525	97
Unknown	21	4	21	4	0	0
* Number of cases registered in both hospital records and DCR (per cent according to cases found in hospital records).						

Table 14: Comparison of the number of prostate cancer patients with reported and confirmed distant metastases at diagnosis and whether they received curative treatment.

HOSPITAL RECORDS		Danish Cancer Registry (DCR)				
M-stage	T-stage	Unknown	Localized	Regional	Distant metastasis	Total
M0	**T1-2**	21	56	6	3	86
	T3	10	11	6	0	27
	T4	2	1	2	2	7
	TX	3	2	3	1	9
M1	**T1-2**	28	19	4	54	105
	T3	18	6	2	39	65
	T4	8	5	2	25	40
	TX	6	4	1	21	32
MX	**T1-2**	49	61	10	8	128
	T3	15	12	1	2	30
	T4	6	3	2	2	13
	TX	8	6	4	9	27
Total		174	186	43	166	569

Table 15: Comparison of clinical stage in hospital records and stage in the Danish Cancer Register for Danish patients diagnosed between May 1st and December 31st 1997, in 8 counties in Denmark.

Out of the 569 cases reported to the DCR, 174 cases were reported as having unknown stage (31%). In hospital records, T-stage could not be determined (TX) for 68 patients. In this group, 9 had no distant metastases (M0), 32 had confirmed distant metastases (M1), and the remaining 27 had unknown dispersion (MX).

Cases with T1-2 tumour that did not undergo further work-up and therefore had unknown metastatic status (MX) were 128, or approximately 23% of all patients. Half of the 128 patients were reported to the DCR as having localised disease.

There was no statistically significant difference in the distribution of M-stage between patients with a date of diagnosis within or exceeding 4 months. Likewise, there was no significant difference in M-stage between rural and urban areas (data not shown).

Paper V – Improved survival for patients with *de novo* metastatic prostate cancer in the last 20 years

Baseline characteristics of the 207 men diagnosed with PC in 1997 and 316 men diagnosed with PC in 2007-2013 are presented in Table 16. Men in the historical cohort had a significantly higher PSA (median PSA: 258 ng/ml versus 158 ng/ml, $p < 0.001$), a more advanced clinical T-stage ($p < 0.001$), and a higher Charlson comorbidity index (CCI, $p = 0.03$) at diagnosis compared to men in the contemporary cohort. In the historical cohort 57% underwent orchiectomy as opposed to only 9% in the contemporary cohort where Gonadotropin releasing hormone (GnRH) agonists were almost exclusively used. Only one patient in the historical cohort received life-prolonging treatment (chemotherapy) compared to 1 in 4 of the cases in the contemporary cohort (Table 17)

Significant differences in overall survival were found between the cohorts, Figure 14. The median survival of the 1997 cohort was 24.2 months (95%, CI:18.3-28.4) compared with 39.4 months (95%, CI: 31.2-46.0) in the 2007-2013 cohort, $p < 0.0001$.

Figure 15 shows the 5-year cumulative incidence of PC-specific mortality was higher for the historical cohort compared to the contemporary cohort, i.e. 72.4% (95%, CI: 66.3-78.5) and 47.2% (95%, CI: 41.1-53.3), respectively ($p < 0.0001$). The median PC-specific survival was 28.4 months (95%, CI: 23.3-33-5) in the 1997 cohort compared with 68.6 months (95%, CI: 55.6-87.7) in the 2007-2013 cohort. In contrast, other-cause mortality remained virtually unchanged with 5-year cumulative incidences of 11.7% (95%, CI: 7.3-16.1) and 20.4% (95%, CI: 15.7-25-2) for men diagnosed in 1997 and between 2007-2013, respectively (Figure 15).

Table 18 shows multivariate Cox regression analysis adjusting for age, pre-treatment PSA, CCI, clinical T-stage and primary treatment, where the results show that men from the contemporary cohort had a 37% reduced hazard of death compared with men from the historical cohort (HR 0.63 [95% CI: 0.47-0.85], $p = 0.003$). In a similar multivariable model, men diagnosed between 2007-2013 had a 43% reduced hazard of PC-specific death compared with men diagnosed in 1997 (HR 0.57 [95% CI: 0.40-0.79], $p = 0.0009$), Table 19.

	1997 cohort n = 207	2007-2013 cohort n = 316	*p* value*
Age at treatment start, years, median (IQR)	74 (68-79)	73 (67-80)	0.61
PSA at treatment start, ng/ml, median (IQR)	258 (83-726)	158 (48-391)	< 0.0001
Charlson co-morbidity index, n (%)			0.03
0	86 (41.5%)	170 (53.8%)	
1	79 (38.2%)	91 (28.8%)	
≥ 2	38 (18.4%)	55 (17.4%)	
Unknown	4 (1.9%)	-	
Clinical tumour category, n (%)			< 0.0001
cT1	12 (5.8%)	73 (23.1%)	
cT2	77 (37.2%)	116 (36.7%)	
cT3	63 (30.4%)	87 (27.5%)	
cT4	39 (18.8%)	27 (8.5%)	
Unknown	16 (7.7%)	13 (4.1%)	
Biopsy histopathology, n (%)			NA
WHO well-differentiated	6 (2.9%)	-	
WHO moderate-differentiated	50 (24.2%)	-	
WHO poor-differentiated	83 (40.1%)	-	
GS ≤ 7	-	61 (19.3%)	
GS 8	-	83 (26.2%)	
GS 9 – 10	-	148 (46.8%)	
Unknown	68 (32.9%)	24 (7.6%)	
Metastasis at diagnosis, n (%)			1.0
M1	207 (100%)	316 (100%)	
First-line treatment, n (%)			< 0.0001
GnRH agonist	48 (23.2%)	281 (88.9%)	
Orchiectomy	118 (57.0%)	27 (8.5%)	
Total androgen blockade	24 (11.6%)	8 (2.5%)	
Androgen receptor inhibitor	15 (7.2%)	-	
Oestrogens	2 (1.0%)	-	

Table 16: Baseline characteristics of the 207 men diagnosed in 1997 and the 316 men diagnosed in 2007-2013 with metastatic prostate cancer in Denmark.

	1997 cohort n = 207	2007-2013 cohort n = 316
Life-prolonging treatments, n (%)		
Total number of patients	1 (0.5%)	81 (25.6%)
Specific life-prolonging treatments, n (%)		
Docetaxel	1 (0.5%)	52 (16.5%)
Cabazitaxel	-	20 (6.3%)
Abiraterone acetate	-	51 (16.1%)
Enzalutamide	-	29 (9.2%)
Radium-223	-	4 (1.3%)
Total number of life-prolonging treatments, n (%)		
0	206 (99.5%)	235 (74.4%)
1	1 (0.5%)	38 (12.0%)
2	-	21 (6.6%)
3	-	14 (4.4%)
4	-	6 (1.9%)
5	-	2 (0.6%)

Table 17: Treatment with life-prolonging treatments among 207 men diagnosed in 1997 and the 316 men diagnosed in 2007-2013 with metastatic prostate cancer in Denmark

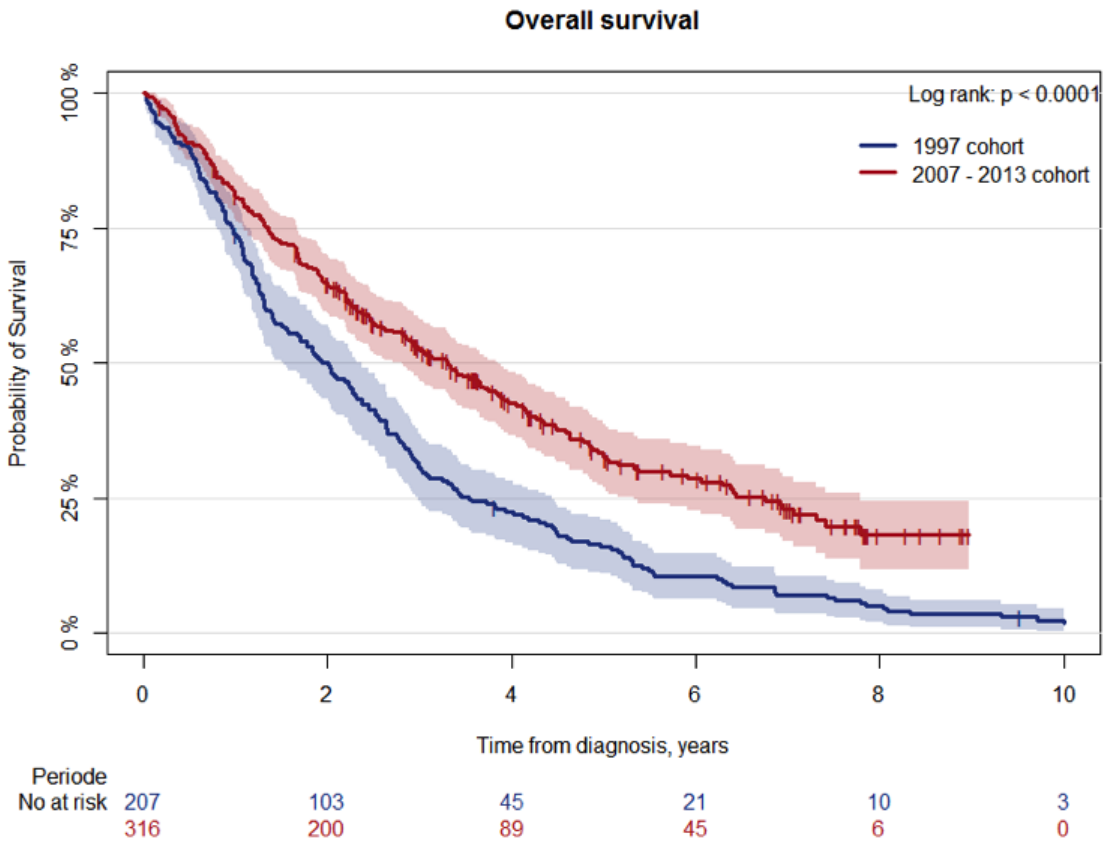


Figure 14: Overall survival stratified by cohort among 207 men diagnosed in 1997 and the 316 men diagnosed in 2007-2013 with metastatic prostate cancer in Denmark.

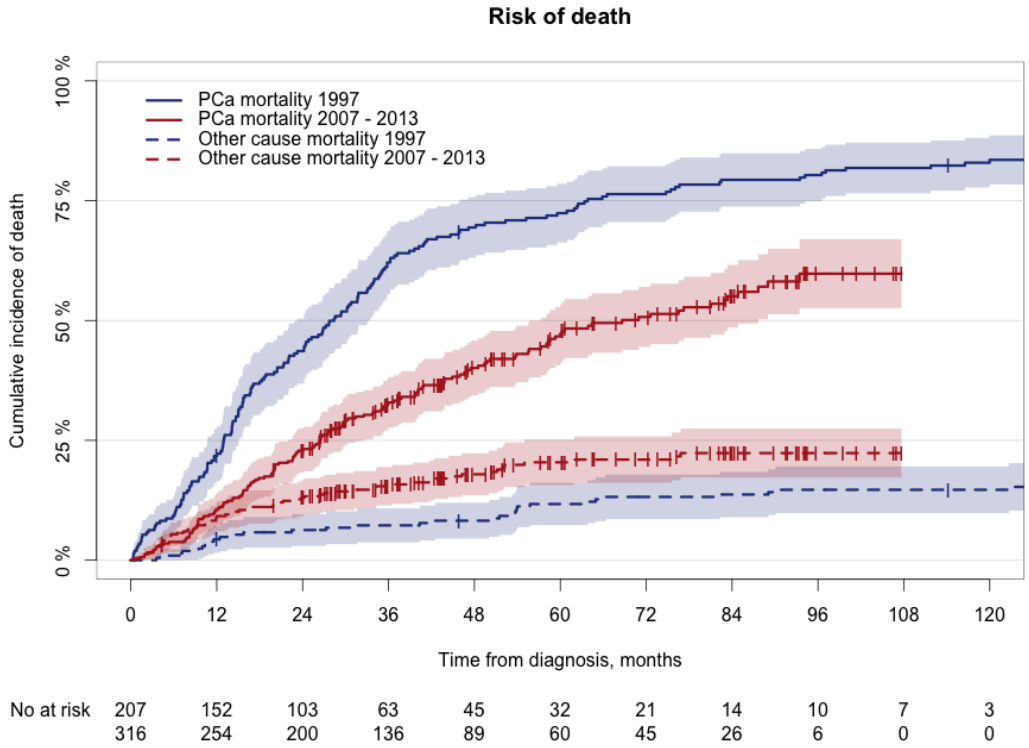


Figure 15: Cumulative incidences of prostate cancer specific mortality (solid lines) and other-cause mortality (broken lines) stratified by cohort among 207 men diagnosed in 1997 (blue lines) and the 316 men diagnosed in 2007-2013 (red lines) with metastatic prostate cancer in Denmark.

	Univariable analyses			Multivariable analysis		
Variable	**Hazard ratio**	**95% CI**	***p* value**	**Hazard ratio**	**95% CI**	***p* value**
Diagnostic group						
1997	1	(ref)		1	(ref)	
2007 – 2013	0.59	(0.48-0.72)	< 0.0001	0.64	(0.48-0.87)	0.004
Age; for 5 years diff.	1.10	(1.04-1.17)	0.002	1.07	(1.00-1.14)	0.04
PSA; for 2-fold diff.	1.12	(1.07-1.17)	< 0.0001	1.11	(1.05-1.16)	< 0.0001
Charlson comorbidity index						
0	1	(ref)		1	(ref)	
1	1.27	(1.01-1.59)	0.042	1.20	(0.95-1.52)	0.13
≥ 2	1.59	(1.22-2.09)	0.001	1.45	(1.10-1.93)	0.009
Clinical tumour category						
cT1	1	(ref)		1	(ref)	
cT2	1.41	(1.02-1.96)	0.04	1.31	(0.94-1.83)	0.11
cT3	1.33	(0.95-1.87)	0.09	1.33	(0.94-1.89)	0.10
cT4	1.50	(1.02-2.20)	0.04	1.27	(0.85-1.90)	0.24
Primary treatment						
LHRH treatment	1	(ref)		1	(ref)	
Surgical castration	1.49	(1.19-1.87)	0.001	0.86	(0.62-1.18)	0.33
Total androgen blockade	1.33	(0.89-1.99)	0.16	1.11	(0.72-1.73)	0.64
Androgen receptor inhibitor	1.12	(0.65-1.94)	0.68	0.75	(0.41-1.39)	0.36
Oestrogens	1.70	(0.42-6.86)	0.46	1.21	(0.29-5.06)	0.79

Abbreviations: CI = confidence interval; PSA = prostate-specific antigen.

Table 18:: Overall survival Cox analyses including 183 men diagnosed in 1997 and 303 men diagnosed between 2007-2013 with complete baseline information

	Univariable analyses			Multivariable analysis		
Variable	**Hazard ratio**	**95% CI**	***p* value**	**Hazard ratio**	**95% CI**	***p* value**
Diagnostic group						
1997	1	(ref)		1	(ref)	
2007 – 2013	0.50	(0.39-0.62)	< 0.0001	0.57	(0.40-0.79)	0.0009
Age; for 5 years diff.	1.05	(0.98-1.12)	0.21	1.01	(0.94-1.09)	0.77
PSA; for 2-fold diff.	1.17	(1.12-1.23)	< 0.0001	1.15	(1.10-1.22)	< 0.0001
Charlson comorbidity index						
0	1	(ref)		1	(ref)	
1	1.18	(0.92-1.52)	0.20	1.14	(0.88-1.48)	0.33
≥ 2	1.04	(0.74-1.47)	0.81	0.93	(0.65-1.32)	0.67
Clinical tumour category						
cT1	1	(ref)		1	(ref)	
cT2	1.25	(0.87-1.79)	0.23	1.14	(0.78-1.66)	0.50
cT3	1.26	(0.87-1.82)	0.23	1.26	(0.86-1.85)	0.24
cT4	1.47	(0.96-2.25)	0.08	1.24	(0.80-1.93)	0.34
First-line treatment						
LHRH treatment	1	(ref)		1	(ref)	
Surgical castration	1.72	(1.33-2.22)	< 0.0001	0.96	(0.67-1.38)	0.84
Total androgen blockade	1.63	(1.06-2.51)	0.03	1.28	(0.80-2.06)	0.31
Androgen receptor inhibitor	1.31	(0.72-2.37)	0.38	0.72	(0.37-1.41)	0.34
Oestrogens	2.30	(0.57-9.32)	0.24	1.38	(0.33-5.84)	0.66

Abbreviations: CI = confidence interval; PSA = prostate-specific antigen.

Table 19: Prostate cancer specific survival – Cause specific Cox analyses including 183 men diagnosed in 1997 and 303 men diagnosed between 2007-2013 with complete baseline information.

After the 82 men who received life-prolonging therapies after progression on first-line treatment were excluded, subgroup analyses confirmed improved survival among men in the contemporary cohort. Therefore, 5-year cumulative incidences of PC-specific mortality were 72.7% (95% CI: 66.6-78.9) and 46.3% (95% CI: 39.3-53.2), respectively, $p < 0.0001$. In the multivariable Cox regression analysis contemporary patients had a 40% reduced hazard of PC-specific death (HR 0.60 [95% CI: 0.43-0.86], $p = 0.009$).

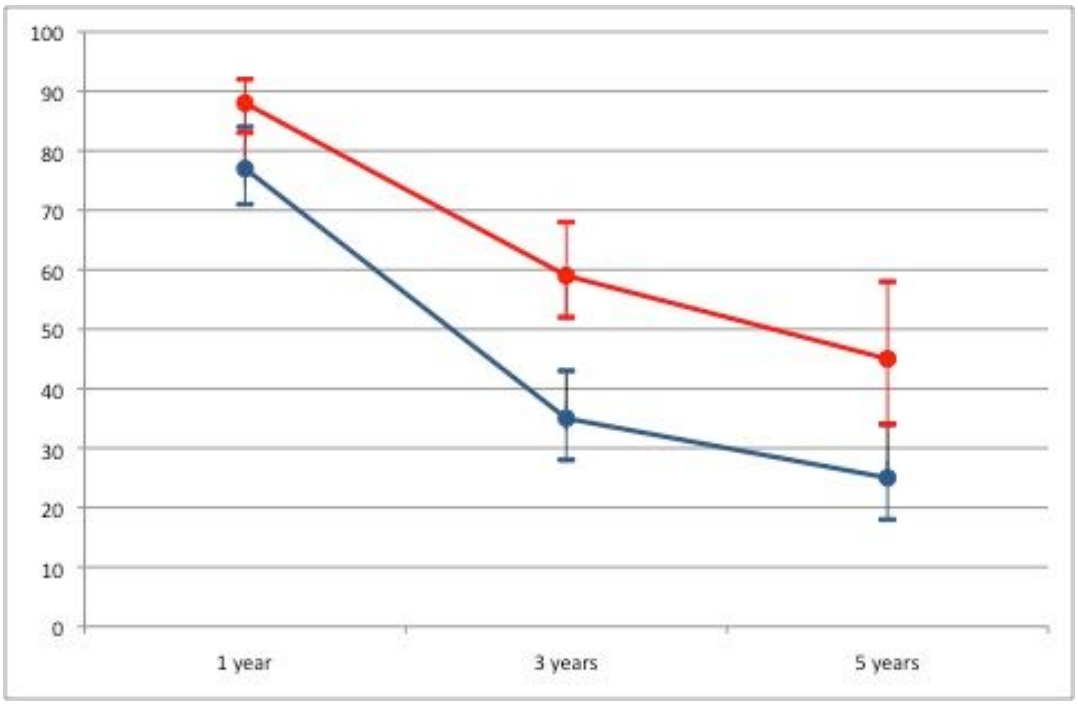


Figure 16: The relative survival of metastatic prostate cancer in patients diagnosed in 1997 (blue line) and 2007-2013 (red line) compared with an aged-matched standardised background population.

The 5-year relative survival improved significantly over time, with an increase from 25% (95% CI: 18-34) for men diagnosed in 1997 to 45% (95% CI: 34-58) for men diagnosed in 2007-2013.

Chapter 3: General discussion and conclusion

MAIN FINDINGS

The results in Paper I showed that the relative survival in the study cohorts was comparable to that in previous population-based studies. Therefore selection bias is unlikely to influence results. Significant differences in excess mortality rates were found across countries, which diminished or disappeared after adjustment for patient characteristics, i.e. metastatic status, clinical tumour (T) stage, and PSA levels. A difference in the proportion of patients with metastatic disease was the main explanation for the differences in survival among countries, while the incidence rates of metastatic cancer were similar.

In Paper II, we found that LUTS were the predominant clinical presentation among patients reported with localised PC in Denmark and Iceland. Diagnosis was commonly confirmed by TURP in Denmark, but by Tru-cut biopsies in Iceland. Icelandic cases were younger; a five-fold higher proportion was diagnosed incidentally and was more likely to have undergone bone imaging, have a normal PSA value and a well-differentiated tumour. Treatment with curative intent and endocrine treatment were more commonly administered in Iceland. By stratifying according to M-stage, M0 cases had comparable outcomes during the first 4 years following diagnosis; thereafter, survival of Danish patients was significantly poorer. A significant difference in survival of patients with unknown metastatic stage (MX patients) was apparent during the whole follow-up period.

Paper III was published in 2007 and showed that the age-standardized (World Standard Population) rate of PC in Denmark increased from 11 per 100,000 in the period 1943-1947 to 38 per 100,000 in the period 1998-2002. Mortality rate increased from 14 per 100,000 in 1953 to 19 per 100,000 in the period 1993-98. Within the last 10 years (before publication in 2007) changes in age distribution and clinical stage in Denmark, especially among younger patients, indicated a shift towards a more aggressive diagnostic policy.

Paper IV showed that the mean age at diagnosis in the Danish cohort in 1997 was 74.6 years. Most patients underwent histological verification (87%), and the date of diagnosis between the DCR and hospital papers matched in 70% of cases. Two out of 33 cases reported to the DCR having undergone radical prostatectomy matched, but 24 of these cases had undergone TURP.

Additionally, 5 cases underwent radical prostatectomy. Sixteen cases were reported to have undergone radiotherapy. Four cases were confirmed in hospital records, but only one case matched. Around 50% of cases reported with disseminated disease matched.

In Paper V, comparisons between a historical cohort and a contemporary cohort showed that at the time of diagnosis, men diagnosed in the period 2007-2013 had less comorbidity, lower PSA level, and lower clinical tumour category compared to men diagnosed in 1997. A great reduction in surgical castration was seen (9% vs 57%) and around 26% of patients received second-line therapy, compared to only one patient in the older cohort. Five-year cumulative incidence of PC-specific death fell from 72% in the older cohort to 47% in the contemporary cohort ($p < 0.0001$). Survival in men diagnosed with metastatic PC has improved significantly over time, with median overall survival of 39.4 months versus 24.2 months ($p < 0.0001$).

GENERAL DISCUSSION

This thesis has reported on epidemiological aspects on PC in Denmark, Iceland and, to some extent, Sweden. It has mainly explored clinical factors, staging, treatment, and outcome after 10 years of follow-up.

Clinical parameters put into context

Papers I and II reported nation-wide epidemiological aspects of PC in Iceland and comparable (a cohort shown to be representative of the whole Danish nation) results from Denmark around the year 1997. Data previously published, based on cancer registry data have lacked clinical information to further explain the differences found between neighbouring Nordic countries. Valid and up-to-date data are essential for epidemiological research, but the validity of the clinical information gathered in the DCR had never been analysed.

The unique population-based follow-up in the Nordic countries provides a preferable platform to view and evaluate trends in incidence, mortality, and survival. Differences in incidence and survival observed between neighbouring Nordic countries have been a matter of intense debate. The Danish health care system has previously received criticism for not providing sufficient quality of medical care, as large survival differences among PC patients were observed, with poorer outcomes Denmark (102) in particular. Perhaps the situation was not as inadequate as once perceived, and lead-time bias and differences in treatment policies may have played a big role.

The Danes were conservative and reluctant towards early case finding (98), and both Paper I and Paper II show that Danish patients had more advanced disease at diagnosis. Large differences in the distribution of clinical T stage, M status, differentiation of tumours, and PSA level at diagnosis were found between the cohorts in Paper I. The percentage of patients with disseminated disease was twice as high in the Danish cohort compared to the Icelandic cohort.(130) Having metastatic disease at diagnosis increased the excess mortality rate ten-fold relative to M0, followed by hormonal treatment, PSA level, and clinical T stage.

As the years passed, this original approach in Denmark may have helped us to put things into perspective. In 1997, we had a country (Denmark) on one side of the spectrum with almost no early case finding, and at the opposite side of the spectrum, we had data from 2 countries (Iceland and Sweden) with more active case finding, although none of the countries had, or have to this day,

implemented official PC screening. As therapy with curative intent was rarely offered in Denmark in the period of the study, this finding reflects less intensive staging.(131)

Even restricting analysis to cases with clinical localised PC in Paper II, we found that the Icelandic cohort still had a significant relative survival advantage compared to the Danish cohort. The Icelandic cases tended to be younger and, compared to the Danish cohort, a five-fold higher proportion of them were diagnosed following an opportunistic PSA test (having stage T1c). Paper II further shows that diagnosis among patients with localised disease was more commonly confirmed by TURP in Denmark but by Tru-cut biopsies in Iceland. This suggests that many asymptomatic middle-aged men in Iceland may have been diagnosed with PC because of increased awareness and opportunistic diagnostic activity. Paper II shows that a higher proportion of Icelandic men underwent work-up with bone imaging. This finding is also consistent with a different approach towards curative therapy.

This thesis shows that a very large proportion of Danish patients had stage MX, which entails that complete staging was not performed. A lack of interest and shortage in supply of curative treatments in Denmark at the time may have played a large role. This unconcern or lack of ambition is, for instance, portrayed in the reporting to the DCR in Paper IV, where reported information on stage and treatment around 1997 was inaccurate. A relatively small discrepancy between the date of diagnosis registered in the DCR and the date found in the hospital records was observed. However, it had only a negligible effect on overall survival.

As the DCR only recorded treatment during the first 4 months following diagnosis, there is a risk of underestimation of actual treatment given. Paper IV demonstrated a considerable “over-reporting” of curative treatment (Table 14). A possible error may have occurred when the physician reported “operation” and did not state whether an operation was attempted to be radical, palliative, therapeutic, or merely diagnostic. Further, it may be a consequence of a misunderstanding in the reporting procedure, i.e. registering palliative radiation therapy as curatively intended or TURP as radical surgery. Again, this may reflect a lack of interest in documentation. The results clearly indicate that clinical data and information on therapeutic procedures in the DCR should be interpreted with caution.

Despite the rising interest and implementation of radical prostatectomies in Denmark around 1997, it is surprising that Paper III showed that almost 25% of young patients were reported with unknown clinical stage. Paper II shows that cases with stage MX are different in Iceland and in Denmark. In fact, many Danish MX patients have a higher tumour burden and more progressive disease,

and if their work-up had been done thoroughly, many of them would probably have been identified with metastatic disease (stage M1). This under-reporting of patients with metastatic disease may jeopardize international comparisons based on register data.

Among Danish cases reported with localised disease, almost 60% had stage MX, compared to 35% of the Icelandic cohort. This further reflects a generally conservative approach towards early detection and different treatment policy in Denmark at the time of the study. It is obvious from the differences in patient characteristics and survival comparison that these cohorts are different, although around 1997, both were reported to their respective cancer registries as localised PC. With increased early case finding in Denmark, and upgrading the DCR since 2004 by making reporting of the TNM status at diagnosis mandatory,(132) it is hoped that staging has become more accurate and detailed. Treatment has been recorded in the National Patient Register through electronic notifications from clinical contacts, and this has presumably made data on treatment more reliable.

Trends in age composition of PC patients

In 1997, Denmark was not entirely free from opportunistic PSA testing. In the study period of Paper III, 1943-2002, incidence rates of PC in Denmark more than tripled. In an earlier study that looked at the incidence trends between 1943-1992, no changes in age distribution or clinical stage were observed that could indicate that the rising PC incidence primarily was due to increased diagnostic activity.(133) So, most of the changes took place between around the mid-nineties to 2002. Paper III showed that the proportion of Danish cases under 70 years had increased from the mid-nineties to the turn of the century. Thus, before around 1995, the age-distribution of PC had been constant in Denmark and incidence therefore rose exponentially with age.

The reported data on staging showed that the number of localised PC only gradually increased from 1963-1967 to around 1988-1992, attributed to a rise in TURP procedures, but stagnated in Denmark in 1989 when pharmaceutical therapy was introduced for BPH. Incidence in Denmark began to rise again in 1995 associated with a sharp rise in PSA testing, although apposing official recommendations ((119) and implementation of RP.

Figure 17 shows that the incidence rate of PC cases in Denmark between the age group 50-59 years increased almost six-fold from 1995 to 2011. In the same period, the rise for 60-69-year olds and 70-79-year olds increased by 29% and 49%, respectively. The slope in PC incidence from 1995 to 2000 was similar for patients 60-69 years old and patients 70-79 years old, but from 2002 to 2006, a

much sharper rise was observed for patients 70-79 years old than in patients 60-69 years old. Incidence for patients 70 years and older peaked in 2006-2007 and has since been falling quite sharply. The incidence for patients aged 60-69 years levelled off in 2010 but was still rising for patients younger than 60 years of age.

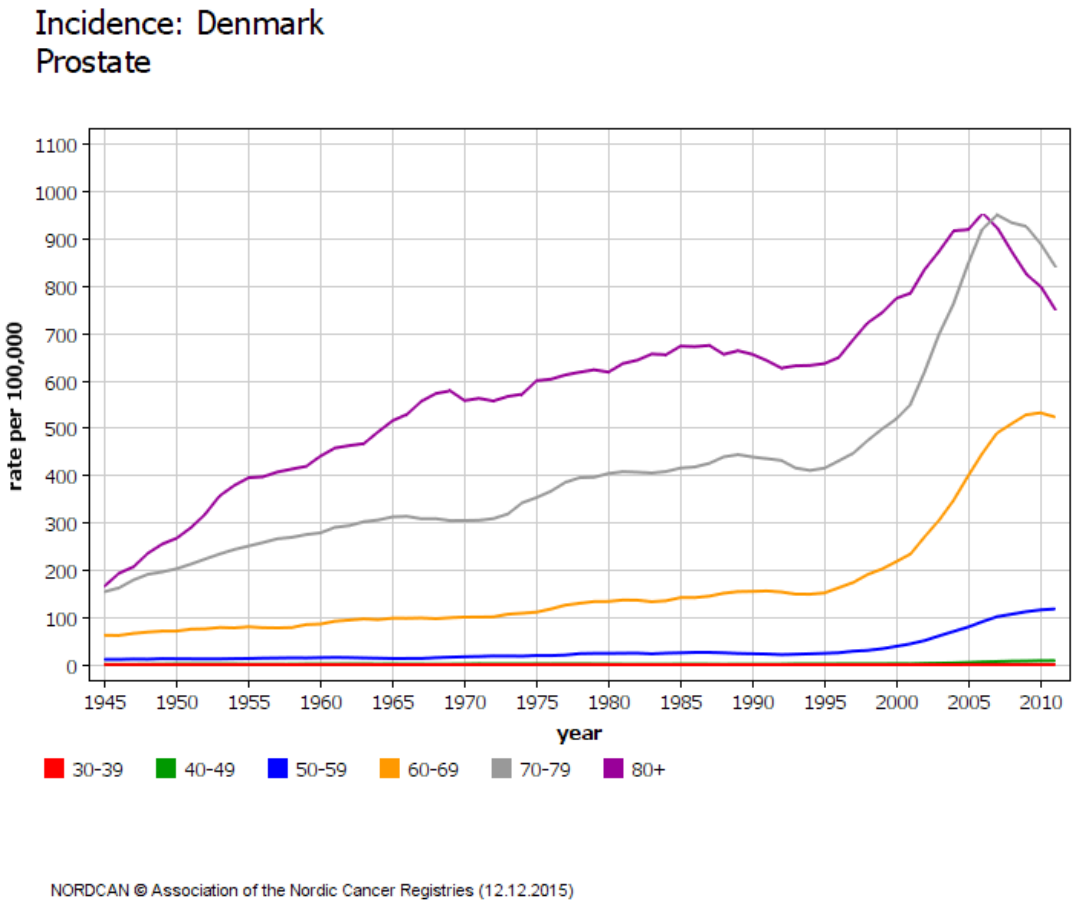


Figure 17: Incidence time trends by age of Danish PC patients.

A trend similar to what occurred in Denmark has been observed in Iceland, although the incidence rate among 60-69-year olds in Iceland has also begun to fall sharply (Figure 18). The fall in incidence among patients in the older generations may be because a majority of them may have been previously tested, leaving fewer potential cases left to test or diagnose. Furthermore, it can be partly due to the fact that they have shorter life expectancy and therefore less effort is laid on early case finding, and this group is rarely offered curative treatment. It is also important to take into account that some physicians may have been more conservative and conscious about avoiding over-diagnosis of men with indolent disease.

Between 2000-2006, PSA tests in Denmark were mostly due to a rise in tests requested by a general practitioner, but the number requested by hospital

specialists remained stable.(119) Perhaps even men up to 79 years of age tend to be more aware of a healthy lifestyle today and may request a PSA test from their general practitioner more often than older men. The rise in diagnostic activity can also be the consequence of the increased number of transrectal ultrasounds with biopsy being performed, which rose ten-fold in the period 1997-2003.(122)

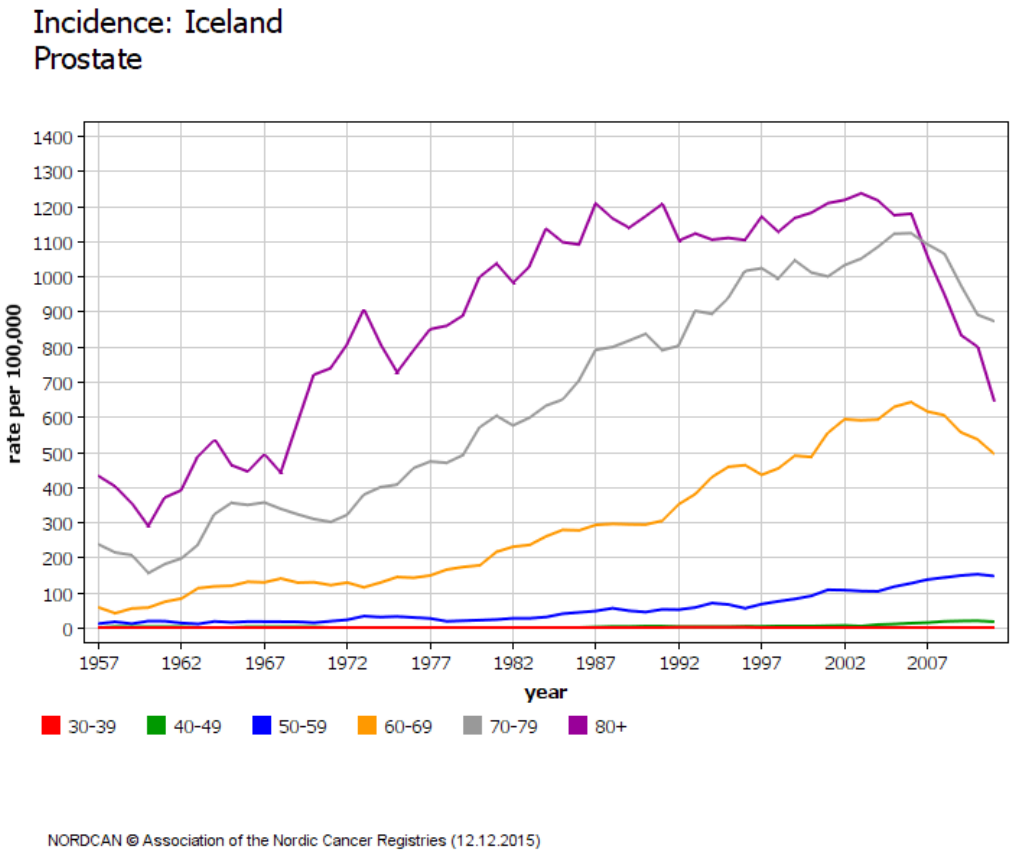


Figure 18: Incidence time trends by age of Icelandic PC patients.

In 2002, Møller et al. tried to estimate the future number of PC cases. In 2007, the incidence was around 20% higher than their 2002 estimate.(134) The rise in incidence and the need for treatment was therefore much steeper. This development had substantial consequences for the health care system and its ability to offer work-up, treatment, and control of PC.

PC diagnostics and management have changed in the Nordic countries during the past few decades. The changes in incidence rates in the 3 countries discussed in this thesis are similar to those observed in Europe and the United States in general, reflecting more widespread use of PSA testing in screening or early case finding.(115, 135) Icelandic urologists were primarily influenced by concurrent practices in the United States and Sweden, where a more aggressive approach towards early case finding has been practiced than in Denmark. The continued and sharper rise in incidence of PC in Iceland was also consistent with a rapid rise in PSA testing in Iceland (Figure 4).(136)

Hormonal and Life-Prolonging Treatments

The majority of PC cases respond to endocrine therapies.(137) Androgen deprivation therapy (ADT) has been the mainstay of advanced PC treatment for decades. Previously, hormonal treatment within 6 months of diagnosis (primary ADT) was widely used for localised PC, especially among the older age groups.(138) This approach may have been influenced by preceding studies that showed borderline survival benefit for PC patients without distant metastases (stage M0) and poor differentiated tumours that received immediate ADT,(139) but later when the study cohorts involved were followed-up for a longer period of time this benefit disappeared altogether.(138, 140)

Conversely, improved overall survival has been reported in patients with locally advanced disease managed with androgen receptor-inhibitors, whereas no improvement was found for patients with clinically localised PC, where a trend towards decreased overall survival was observed.(141) Primary ADT is now only recommended to prevent imminent symptoms caused by disease progression or to palliate symptoms.(138) In addition, it can be used in combination with radiotherapy where it unequivocally improves survival.(142)

Patients with disseminated PC have understandably significantly higher excess mortality due to their disease progression but perhaps also because they are likely to receive ADT early and complications to ADT may partly increase mortality.

Most prostate cancers treated with ADT later become castration resistant (CRPC), i.e. acquire the capability to proliferate despite having reached castrate levels of testosterone.(137) During the last decade, a number of therapies have demonstrated survival benefit for CRPC patients in randomised controlled trials.(143) Paper V showed better overall survival and PC-specific survival for the contemporary cohort but other-cause mortality was more or less unchanged. As only 25.6% of the contemporary cohort received second-line therapy and the survival gains reported in phase 3 trials are in the range 1.9-4.2 months,(144-147) so lead-time bias and differences in metastatic burden are likely to have contributed the most to the survival benefit. The combination of chemo-hormonal therapies has demonstrated significant survival improvement of patients with metastatic PC (148-150) and are more frequently used now when primary therapy fails.

Effects of unofficial PC screening

Swedish physicians have adopted a more aggressive attitude to screening, and Swedish centres participated in the European Randomized Study of Screening for Prostate Cancer (ERSPC). Nevertheless, a general screening program has not been introduced in Sweden (151) or Iceland.(152) The Danish Urological

Society has, throughout the years, not recommended PSA testing of asymptomatic men unless the individual has a genetic disposition for PC. This approach is still unchanged in their most recent guidelines from March 2015.(153)

PC incidence reached a peak in Sweden in 2005 and Iceland in 2006, and has since then been falling in both countries but more sharply in Iceland. In Denmark, incidence of PC began to fall slightly in 2009.(77) Meyer at al. suggested that the true incidence rate of lethal PC in the Nordic countries remained unchanged from 1965-2006, whereas the differences in incidence rates were the consequence of differences in diagnostic intensity, mainly towards PSA testing and thus the differences in incidence rates were mainly explained by "over-diagnosis" of nonlethal PC.(154) This is supported by the stage migration discussed above and in Papers I and II.

The subsequent fall in incidence might be a consequence of first-time testing, which has been shown to have a profound effect on incidence, despite overall increased testing rates (86). Perhaps a declining interest in case finding has also played a role.(155) Moreover, as autopsy procedures have generally been diminishing in most Western countries, it is possible that some PC cases have remained undiagnosed.

Stage Migration

Stage migration is the upstaging of cancers because of more sensitive imaging tests and occurs because each stage of a malignancy has a different degree of aggressiveness.(156) In countries with widespread PC screening, there has been a trend towards strong stage migration. In the United States' CaPSURE database, the proportion of cases diagnosed with low-risk PC increased from 30% to 45% between the periods 1989-1992 to 1999-2001, respectively.(157) During the period 2004-2005, a study from the Surveillance, Epidemiology and End Results (SEER) database showed that 94% of cases diagnosed in the United States had localised PC (stages T1-T2).(158) In high-income countries, incidence trends initially increased with the rise in the use of TURP procedures and, from the mid-to late 1980s, as a result of PSA testing.(85, 159, 160) Stage migration can spuriously increase stage-specific survival rates (161) but does not change overall survival rates for a given cancer.(162)

A Swedish study based on population-based NPCR data demonstrated a substantial stage migration of PC in Sweden from 1998 to 2011. Over time, patients had lower PSA levels; the percentage of PC patients diagnosed with stage T1c tripled, and more patients had smaller tumour volume. Further, during

the study period the percentage of low- and intermediate-risk disease doubled (from 14% to 28%), and the percentage of distant metastases fell from 25% to 11%.(40) Stage migration previously observed around 1997 seems to have continued in Denmark, as recent Danish data show that 13.7% of PC patients present with stage M1.(163) Currently, clinical staging has become more complete because of full implementation of curative treatment and a general rise in awareness of PC.(164)

Early detection identifies relatively low-risk cancers that grow slowly, have the longest asymptomatic phase and have the most favourable prognosis. This phenomenon is known as length bias and is commonly picked up by screening and as a consequence of length bias these screen-detected cancers appear to have the longest survival times. A Swedish study based on NPCR material showed that conservatively low-risk PC patients that were followed-up for 15 years had a 9% risk of dying of PC and a 50% other cause mortality risk.(165)

Overdiagnosis is the most extreme case of length bias and is present when a cancer is discovered that was never destined to progress at all or too slowly to ever become the cause of death for the individual involved. The rise in PC incidence in the U.S. peaked in the early 1990s, fell after that and reached a plateau at a higher level than in before the PSA era, consistent with overdiagnosis.

Mortality and Survival

Relative survival (RS) is the observed survival divided by the expected survival based on population mortality. In this thesis RS refers to survival from the prostate cancer if no other cause of death is present. Improved survival reflects real progress when it is accompanied by a decrease in disease burden, but can also occur even if disease burden increases.(156)

Relative survival for PC has evolved in the same way as incidence, while mortality rates were relatively constant from 1983 to 1998 (102) but have clearly been falling since the turn of the century (Figure 3b).(77) Curative intended therapy in the Nordic countries was not fully implemented in the late 1980s and was adopted in Denmark somewhat later than in the other Nordic countries.(112) Therefore, a rise in mortality rates in all the Nordic countries in the early 1990s may reflect higher rates of clinically symptomatic disease. However, the initial rise in mortality may partly be explained by attribution bias, where the cause of death is attributed to PC even when other diseases carrying high mortality are also present. According to Bray et al., little association between the rise in

incidence in the late 1990s and the recent reduction in mortality has been found.(115)

Regardless of treatment, survival is closely associated with prognostic factors such as stage, histopathology, and PSA level at diagnosis.(166-169) Paper I showed that the difference in excess mortality between Denmark and Sweden (which was used as the reference) virtually disappeared after adjusting for metastatic status at diagnosis.(130) Icelandic patients were more frequently offered curative therapy. The SPCG-4 study demonstrated a survival benefit for younger patients (< 65 years old) managed with curative intent compared to watchful waiting.(170, 171) The practice of radical surgery in Iceland may have improved survival and reduced mortality for some younger PC patients. A study of over 18 thousand men that underwent RP at a U.S. tertial referral centre showed that all-cause mortality was half what it was in the general U.S. population, and death rates were especially low from cardiovascular disease, diabetes and chronic respiratory diseases.(172)

A Swedish study showed that among men with low-risk PC 45% of patients without comorbidity underwent RP compared to only 19% of men with severe comorbidity.(173) In Sweden even work-up with bone scan was more often performed among individuals with higher socioeconomic status. Amongst the subgroup of them with localised disease the likelihood of undergoing RP was higher, and both their overall mortality and PC-specific mortality were lower than for individuals with low socioeconomic status.(174) Thus, men who undergo RP are often a more selective group of healthy men, and also for individuals with a higher socioeconomic status.

Improved PC survival can occur with mixed changes in disease burden. A fall in mortality represents a decrease in cancer burden but a simultaneous increase in incidence can cause a rise in cancer burden. Several biases are introduced by early detection of a disease, especially cases of incidental detection, and they explain why survival can increase without delaying or preventing a single death. Apart from length bias and overdiagnosis, lead-time bias is involved when early detection moves the time of diagnosis back in time and inflates survival. The introduction of an effective screening program leads to earlier detection of lower-stage tumours and this can both affect stage-specific survival and improve overall survival rates.(162)

Paper I showed that Danish patients with M1 disease had significantly poorer survival rates than their Swedish counterparts. Stratification by M status showed no difference in survival rates between Iceland and Sweden. Men with low-risk PC are often selected by early detection and have been shown to have lower 10-year all-cause mortality than healthy controls (that do not have PC), first and foremost because of lower cardiovascular mortality. Conversely, men with

intermediate to high risk PC the PC mortality rate was substantial irrespective of comorbidity levels.(175) Similarly, patients with asymptomatic metastatic PC are likely to have a better prognosis, which would thus reduce excess mortality among M1 patients, with the so-called "Will Rogers phenomenon".(176) The same phenomenon has also been observed in Gleason grade assessment between two time periods. Albertsen et al. showed that there was a shift to higher tumour grades with contemporary evaluation (in 2002-2004) compared to earlier evaluation (in 1990-1992) of the same histology slides and by stratifying survival by Gleason score, all tumour groups appeared to have improved outcomes, solely by rereading the biopsy slides and the assignment of a updated version of the Gleason score.(176)

The Danish cohort with metastatic PC (stage M1) in Paper I, the very same cohort as the historical cohort in Paper V, had a median overall survival of 24 months, which was comparable to previous Danish results.(177) The contemporary cohort of Paper V had approximately 40% increase in overall survival. Paper V shows that between the two time periods studied a shift towards more aggressive treatment of PC has occurred where only 2% of men diagnosed in 1997 received curative treatment increasing to 33% of cases diagnosed in 2007-2013. Some of the survival benefits can be attributed to lower median PSA levels, lower tumour burden, and lower metastatic load in the contemporary group. Active case finding and, consequently, increased diagnosis of latent PC explains part of the improved survival and contribute to lead-time bias.(103, 166, 178). Nevertheless, the introduction of new life-prolonging treatments has also contributed to longer survival. The sustained difference in prognosis between the historical and contemporary cohorts after excluding the 82 patients who underwent life-prolonging therapies, underline the role of lead-time bias but may also partly be influenced by reclassification of tumour grade through Will-Rogers phenomenon effects on survival benefit.

"Reverse stage migration"

Recently, a study conducted by Reese et al. on PC patients reported to the Pennsylvania Cancer Registry between 1992 and 2012 described their recent epidemiology trends as "reverse stage migration". The study showed that age-adjusted incidence rates, especially for localised PC, had been relatively stable from 1994 to 2007, but thereafter fell significantly. Mortality rates in 1992 to 2012 declined steadily but there was no significant change over time.(81)

Age-adjusted incidence rates for localised PC began to fall precipitously in 2008 for Caucasian and in 2009 for African American men but since the late 1990s the incidence of locally advanced and metastatic disease had remained

relatively stable. Thus, the percentage of cases diagnosed with regional or distant disease increased. Reese et al. concluded that incidence decreased primarily because of a decrease in PSA-based screening, which was probably a consequence of recommendations issued in 2008 by the USPSTF, where PSA screening was not recommended for men over 75 years of age.(109) Fewer patients were diagnosed with early-stage disease and correspondingly a shift occurred towards more patients presenting with advanced PC at diagnosis. The continued decline in PC mortality was attributed to the lag between incidence and mortality because of the prolonged clinical course of PC but also because of effective new line treatment for advanced disease, similar to what we have shown in Paper V in this thesis.(81) In 2012 the USPSTF extended their previous recommendation to all age groups.(110) Since, PSA screening has declined for all age groups, overall prostate biopsy rates and PC incidence rates have significantly decreased shifting toward higher grade and higher stage upon diagnosis. The updated report by the USPSTF from February 2017 raises concerns about this development and point out that long-term follow-up is necessary to provide a better understanding of the implications of their previous recommendations.(179)

A decrease both in incidence and mortality trends in the Nordic countries are ongoing but whether this epidemiological trend of reverse stage migration in the U.S. will be observed in the Nordic countries in the future is yet unknown.

STRENGTHS AND LIMITATIONS

The strength of the study is that it is carried out in 3 Nordic countries with similar health care systems that are based on equal access. All cases were recruited by being reported to the cancer registry in their respective country, making selection bias negligible. Follow-up is complete and exceeds ten years. All medical data from Denmark and Iceland in this study were retrieved and recorded by the same physician, using a pre-defined questionnaire, therefore the risk of inter-observer bias is negligible. The Swedish data were adjusted from Swedish databases to fit the other data by the same physician.

Limitations include the retrospective and observational nature of the study. Differences in PC awareness, referral patterns and available treatment options were apparent between countries involved and even between time periods in Denmark. A pitfall that can make this comparison difficult is that when accuracy in reporting tends to be more precise or change over time and historical data may be difficult to compare to more recent patient cohorts. This may have resulted in inter-cohort tumour differences and confounders that are not completely accounted for in the statistics. The extent of biases involved in early detection, e.g. lead-time bias, length bias and overdiagnosis, are difficult to assess exactly as well as other unmeasureable confounders involved. Because of the retrospective study design, it was impossible to adjust for differences in histological grade between Denmark and Iceland, but having had this information would have made the comparison more elaborate.

CONCLUSIONS

Paper I: Register-based studies of the relative survival of PC patients are influenced by national differences in clinical presentation at diagnosis. Differences in the proportion of patients with metastatic spread explained most of the difference in relative survival among patients in Denmark, Iceland, and Sweden. Future country comparisons of relative survival should include adjustment for differences in patient characteristics, such as stage, prostate-specific antigen level, and screening intensity.

Paper II: Icelandic cases were diagnosed with earlier disease and underwent more rigorous work-up. More Danes had undefined M-stage (MX) with lower survival, indicating a larger tumour burden. Administration of curative treatment, regular focus on treatment options, and perhaps earlier implementation of endocrine therapy, may have contributed to better relative survival in Iceland throughout ten years of follow-up.

Paper III: A rise in incidence of PC in Denmark from 1993 to 2002 was most likely explained by an increase in diagnostic activity, presumably as unsystematic PSA-based "grey-zone screening", despite the national recommendation for PSA-based screening for PC.

Paper IV: Reported information on stage and treatment around 1997 was inaccurate. If future comparisons on outcome are to be considered reliable, it is imperative to evaluate the information beyond only the number of cases.

Paper V: Survival in men diagnosed with metastatic PC has improved significantly over time. The improved survival can in part be explained by lead-time bias but also by the effects of new life-prolonging treatments.

FURTHER DIRECTIONS

In recognition of the extensive rise in incidence of PC during the last 25 years, following the introduction of prostate specific antigen (PSA), most Western countries are already faced with an epidemiologic shift from a symptomatic and more aggressive disease to growing cancer burden of chronic disease.

Good-quality epidemiologic data will always be essential in cancer research. Survival of PC patients is related to several factors, e.g. TNM-staging, histological grade, PSA level, and the patient's age. Therefore, cancer registries will benefit tremendously by including clinical data that is collected and registered in the same way. Whether the change in registration procedure in Denmark has increased the validity of clinical information in the DCR must be assessed by a new study.

As new clinical advances are emerging, e.g. immunotherapies targeting tumour-associated antigens, it is invaluable to integrate these new findings in the current therapeutic scenario with valid clinical data.

The next step would be to carry out a new study similar to this one to assess the current clinical status of PC in Denmark and Iceland. One would expect that the differences in factors, e.g. TNM-stage, histological grade, PSA level, and survival, have disappeared or at least decreased considerably. Paper V has given a limited insight, where survival has increased considerably. This finding crystallizes the importance of the clinical data of this thesis. The data may be old, but it is necessary to know where we came from to know where we are heading and to assess progress in the future.

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Paper I

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Differences in survival from prostate cancer in Denmark, Iceland and Sweden

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KEYWORDS
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Abstract ***Introduction:*** Register-based studies have shown large survival differences among prostate cancer patients in the Nordic countries. The aim of this study was to determine the background of such differences in Denmark, Iceland and Sweden.

Material and methods: Patients with prostate cancer were identified through population-based cancer registers in the three countries. Clinical findings at diagnosis were retrieved from hospital records. In Sweden, clinical information was gathered from regional population-based prostate cancer registers. Country-specific incidence and excess mortality rates were compared, with adjustment for prognostic factors.

Results: The relative survival in the cohorts was comparable to that in previous population-based studies. Significant differences in excess mortality rates were found across countries, which diminished or disappeared after adjustment for patient characteristics, i.e. metastatic status, clinical T stage and prostate-specific antigen level. A difference in the proportion of patients with metastatic disease was the main explanation of the differences in survival among countries, while the incidence rates of metastatic cancer were similar.

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Discussion: Register-based studies of the relative survival of prostate cancer patients are influenced by national differences in clinical presentation at diagnosis. Differences in the proportion of patients with metastatic spread explained most of the difference in relative survival among patients in Denmark, Iceland and Sweden. Future country comparisons of relative survival should include adjustment for differences in patient characteristics, such as stage, prostate-specific antigen level and screening intensity.

1. Introduction

A recent Nordic study showed large differences in relative survival and excess mortality after prostate cancer with Danish patients having the poorest prognosis.[1] These findings confirmed those of other studies that showed that Danish prostate cancer patients had poorer survival than those in other Nordic or European countries.[2–4] The Nordic studies[1–3] were based on information from population-based cancer registers, which are validated and reliable in terms of the cases recorded[5–7] but do not include clinical information. The results may therefore reflect differences in treatment, in diagnostic strategy or in screening for prostate-specific antigen (PSA), which result in clinical differences that may explain differences in survival. To evaluate the impact of these factors, a study was conducted with register-based data and also clinical information.

2. Material and methods

Age at diagnosis and clinical findings (TNM stage, histological findings, PSA at diagnosis and primary treatment) were ascertained for three population-based patient cohorts.

In Sweden, all cases of prostate cancer diagnosed in 1997 were identified in the Swedish Cancer Register. Clinical findings and information on primary treatment were retrieved from population-based regional prostate cancer registers in the Uppsala–Örebro and Western regions,[8] covering almost 99% of all new cases in these regions in 1997. In Denmark, all cases diagnosed in the last 8 months of 1997 were identified in the Danish Cancer Register. Hospital records for patients living in eight of the 16 counties of Denmark were retrieved, and clinical findings and information on primary treatment were collected with a questionnaire. In Iceland, all cases diagnosed in 1996–1998 were identified in the Icelandic Cancer Register. As in Denmark, hospital records were retrieved and clinical information collected.

Patients under 90 years of age with prostate cancer recorded as the first primary tumour (excluding non-melanoma skin cancer) were included. Those in whom prostate cancer was detected incidentally at autopsy or only mentioned on a death certificate were excluded. The date of diagnosis was obtained from each cancer register. Patients were followed-up until death or emigration using their personal identification number, which is issued to all residents of Nordic countries at birth or the time of immigration. They were followed-up for death through 31st December 2008 and censored if they emigrated. Only the month and year were available for date of diagnosis and death.

Tumour (T) stage according to the UICC 2002 TNM classification[9] was retrieved from patient records or prostate cancer registers. Positive lymph nodes (N+) were recorded if either lymphadectomy or imaging was positive; patients were considered to be lymph-node negative if they had not undergone lymphadectomy. Patients were categorised as having metastasis (M+) if they had a positive bone scan and/or positive findings on X-rays. PSA values before treatment were registered. Histopathology results were reported as either World Health Organization (WHO) grade or Gleason score.[10,11] Therapy with curative intent was recorded if a patient had undergone radical prostatectomy, external radiation or brachytherapy. Patients managed by 'watchful waiting' were recorded as having had no primary therapy.

Relative survival was calculated as the ratio between the observed and the expected survival based on population mortality. The observed survival was estimated by the actuarial method, and expected survival by the Ederer II method.[12] Relative survival is interpretable as survival from the cancer if no other cause of death is present. Country-specific population mortality rates were derived from the Human Mortality Database (www.mortality.org). To facilitate comparisons, age standardisation was used, with the weights of the International Cancer Survival Standard, as in the Nordic cancer survival study.[13] Relative survival was modelled using additive hazards or excess mortality rates. The follow-up intervals were 0–0.25, 0.25–1, 1–2, 2–3, 3–4 and 4–5 years after diagnosis; however, as the excess mortality was nearly constant throughout follow-up, we present excess mortality only for the first 5 years.

Two-factor models containing country and one risk factor at a time were fitted. As the M stage appeared to have the greatest effect, analyses were repeated after stratification for M stage.

Relative excess mortality rate ratios (RERs) with 95% confidence intervals (CIs) for Denmark and Iceland relative to Sweden were calculated, as were RERs for risk

factor levels, mainly relative to the level with the largest number of patients.

The excess mortality risk was modelled in a generalised linear model with a Poisson error structure fitted to collapsed data, using exact survival times. We used SAS macros supplied by Dickman et al.[14] Estimates were made in SAS version 9.2.

3. Results

Table 1 shows the numbers of cases and the criteria for exclusion before analysis. In total, 3176 patients under the age of 90 years with newly diagnosed prostate cancer were included. Table 2 shows the relative survival in the three cohorts and that in the population-based Nordic Cancer Survival study.[1]

Table 3 summarises clinical information by country. For each factor, a test for homogeneity in distribution between countries is presented, which shows significant differences in the distribution of the factors studied. Table 3 also shows the relative prognostic impact of each level of the factors in further analyses adjusted for country. No systematic correlations between age and clinical characteristics were found.

The proportion of Danish patients with metastases at diagnosis was more than twice that in Iceland and Sweden. Lymph node staging had been performed in only a limited number of cases. Significant differences between countries in clinical T stage and PSA level were found, Danish patients having on average higher T stage and PSA levels. The histological classification system used differed between countries: Both WHO grade and Gleason score were recorded for about 50% of patients in Sweden, mainly WHO grade for Danish patients and Gleason scores for Icelandic patients. Danish patients had statistically significantly more poorly differentiated tumours. Attempts to transform WHO grade to Gleason score in the Swedish data were futile. Therapy with curative intent was used significantly more frequently in Iceland and Sweden than in Denmark (Table 3).

The relative prognostic effect of clinical factors and treatment within the first 6 months of diagnosis was determined by analysing the 5-year relative excess mortality rates for each factor, adjusted for country. Age at

Table 1
Inclusions and exclusions in study cohorts of patients with prostate cancer diagnosed in and around 1997 in Denmark, Iceland and Sweden.

Distribution of inclusion and exclusion criteria	Denmark	Iceland	Sweden
Prostate cancers in cohorts from cancer registers or regional clinical databases	675	438	2566
Exclusions based on register information			
Prostate cancer diagnosis not confirmed by pathology report	–	–	17
Incidental finding at autopsy or death certificate only	18	12	65
Previous or simultaneous other cancer diagnosis	72	48	165
Not in database at time of registration	10	–	–
Hospital records read	575	388	2319
Exclusions based on hospital records/National Prostate Cancer Register (Sweden)			
Previously diagnosed	4	–	2
Diagnosis altered after pathological revision	2	1	–
Incidental finding at autopsy	1	–	–
Previous or simultaneous other cancer diagnosis	–	2	–
Not hospital record found/no in National Prostate Cancer Register	3	–	26
Patients eligible, all ages	565	385	2291
Patients included (age < 90 years)	549	374	2253

Table 2
Age-standardised relative survival (RS) and 95% confidence interval (CI) in a cohort study of prostate cancer patients in Denmark, Iceland and Sweden in 1997 and in the national cancer registers (CRG) from the Nordic Cancer Survival study 1994–1998.[1]

Study	No. of patients	5-Year RS (CI)	10-Year RS (CI)
Denmark			
Study cohort	565	43 (38–49)	24 (19–30)
CRG	7616	42 (40–45)	22 (21–24)
Iceland			
Study cohort	385	75 (67–84)	65 (56–75)
CRG	709	76 (71–82)	63 (57–68)
Sweden			
Study cohort	2291	72 (66–78)	52 (47–58)
CRG	29,116	72 (71–74)	52 (51–53)

Table 3
Patient characteristics in a prostate cancer cohort study 1997 in Denmark, Iceland and Sweden and the relative prognostic impact of patient factor levels estimated as relative excess mortality rate ratios (RERs) adjusted for country.

Patient factor	Denmark ($n = 549$) (%)	Iceland ($n = 374$) (%)	Sweden ($n = 2253$) (%)	Test for homogeneity (p)	RER (95% CI)	Test for effect of factor (p)
Age at diagnosis (years)				0.005		0.00988
40–59	5	5	6		0.93 (0.67,1.29)	
60–69	21	30	24		0.77 (0.62,0.96)	
70–79	45	45	46		1	
80–89	29	20	25		1.23 (0.96,1.57)	
Clinical T stage				⩽0.0001		⩽0.00001
T0–1	16	29	22		0.41 (0.24,0.71)	
T2	40	47	31		1	
T3	22	18	36		2.42 (1.90,3.08)	
T4	11	5	8		4.49 (3.41,5.91)	
TX	11	1	2		2.45 (1.65,3.65)	
N stage				⩽0.0001		
N0	2	5	13			
N+	4	7	2			
NX	94	89	84			
M stage				⩽0.0001		⩽0.00001
M0	23	56	40		1	
M+	43	20	19		10.3 (7.49,14.2)	
MX	34	24	41		2.06 (1.43,2.97)	
PSA (ng/ml) at diagnosis				⩽0.0001		⩽0.00001
0–3.9	3	9	5		0.29 (0.07,1.18)	
4–9.9	5	19	15		0.22 (0.07,0.67)	
10–99.9	38	51	53		1	
⩾100	39	17	23		4.34 (3.50,5.37)	
Unknown	15	5	4			
Gleason score				⩽0.0001		⩽0.00001[a]
2–5	6	42	19		0.03 (0.01,0.19)	
6–7	9	35	20		0.27 (0.19,0.39)	
8–10	13	16	11		1	
Unknown/not reported	72	8	51			
WHO grade				⩽0.0001		⩽0.00001[b]
Well differentiated	15	2	28		0.38 (0.23,0.62)	
Moderate	21	1	41		1	
Poorly differentiated	25	1	25		2.70 (2.15,3.39)	
Unknown/not reported	40	97	6			
Hormone treatment <6 months				0.002		⩽0.00001
Yes	45	44	52		5.89 (4.43,7.82)	
No	55	56	48		1	
Treatment with curative intent				⩽0.0001		⩽0.00001
Yes	2	18	13		0.01 (0.00,16.4)	
No	98	82	87		1	

PSA, prostate-specific antigen; WHO, World Health Organization
[a] Only Iceland and Sweden.
[b] Only Denmark and Sweden.

diagnosis had only a minor effect. M+ disease increased the RER 10-fold relative to M0. Increasing tumour burden, either as higher T stage or PSA level, increased the risk. The effect of clinical T stage was less pronounced in Denmark than in Iceland and Sweden (data not shown). The RER increased with increasing Gleason scores in Iceland and Sweden, while in Denmark and Sweden the RER increased with less differentiated tumours in the WHO grade. Hormone therapy within the first 6 months was associated with a nearly 6-fold increase in RER. Therapy with curative intent was associated with a reduced risk (RER = 0.01; 0.00;16.4).

Fig. 1 shows the 5-year excess mortality rate ratio for Danish and Icelandic patients relative to Swedish

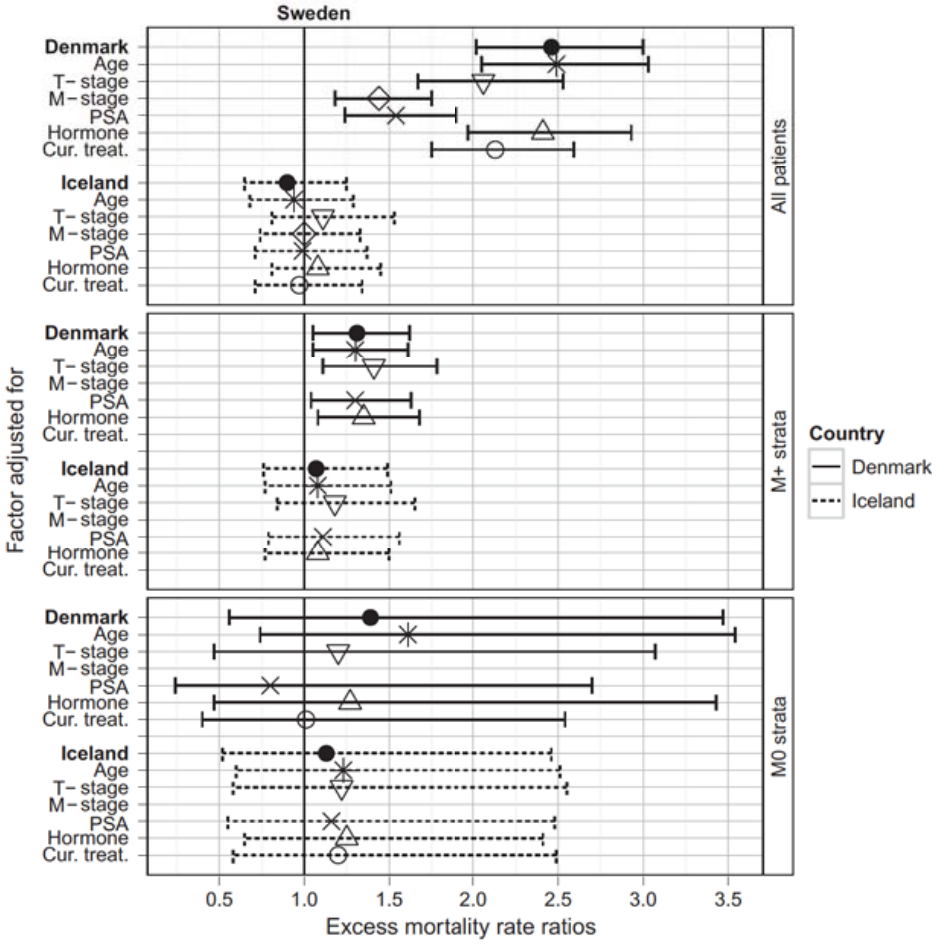

Fig. 1. Five-year relative excess mortality rate ratios (RERs) for prostate cancer in 1997 in Denmark and Iceland, relative to Sweden, overall and adjusted for each prediagnostic characteristic or treatment factor for all patients and stratified by metastatic status (M+ and M0).

patients, overall and adjusted for each of the pre-diagnostic characteristics age, clinical T stage, M stage, PSA level at diagnosis and treatment within 6 months with either hormones or curative intent therapy. These rates are shown for all patients and stratified by M status.

Overall, significantly greater relative excess mortality was found for Danish than for Swedish patients (RER = 2.46; 2.02;3.00), but not for Icelandic patients (RER = 0.90; 0.65;1.25). For Danish patients adjustment for M status gave the largest decrease (RER = 1.44; 1.18;1.75) and adjustment for PSA resulted in a slightly higher RER (1.54; 1.24;1.90). Adjustment for T stage or curative intent therapy had no significant effect. Hardly any effect was seen after adjustment for hormone treatment or age. In a comparison of Icelandic and Swedish patients, none of the factors had a significant effect.

Stratification by M status reduced the ratio between the Danish and the Swedish excess rates to 1.31 (1.05;1.62) for the M+ strata and 1.39 (0.56;3.47) for the M0 strata. Additional adjustment for other factors had only minor effects. In the comparison of Iceland and Sweden, only small, non-significant effects were seen after stratification by M status.

Danish patients who were not evaluated for metastatic disease had significantly higher PSA levels or unknown PSA than Icelandic and Swedish patients. The RERs for patients with unknown M status with PSA $\geqslant$50 or unknown were 7.33 (3.79;14.2) and 5.19 (2.37;11.4), respectively, relative to those with PSA level less than 50 (Table 4).

The age-standardised incidence rates in the four cohorts stratified by M status are shown in Table 5. No difference was found in the rates of metastatic prostate cancer among the cohorts. The rates for M0 prostate cancer were highest in Iceland, followed by both Swedish regions, while Sweden had the highest rates of unknown metastatic status.

4. Discussion

Prostate cancer diagnostics and management have changed in the Nordic countries during the past few decades. The countries have similar health care systems, with open, equal access; however, management of prostate cancer differs markedly. PSA screening is not recommended in Denmark.[15] Although Swedish physicians have adopted a more aggressive attitude to PSA

Table 4
Distribution of prostate-specific antigen (PSA) level and relative excess mortality rate ratios (RERs) among patients with unknown metastatic level in a prostate cancer cohort study, 1997, in Denmark, Iceland and Sweden and relative prognostic impact of PSA-level (RER) adjusted for country.

PSA at diagnosis (ng/ml)	Denmark ($n = 187$) (%)	Iceland ($n = 91$) (%)	Sweden ($n = 931$) (%)	Test for homogeneity (p)	RER (95% CI)	Test for effect of factor (p)
				⩽0.0001		⩽0.0001
<50	38	71	67		1	
⩾50	35	14	27		7.33 (3.79,14.18)	
Unknown	27	14	6		5.19 (2.37,11.35)	

Table 5
Age-standardised incidence rates per 100,000 by metastatic status for four cohorts in a prostate cancer cohort study, 1997, in Denmark, Iceland and Sweden.

Cohort	Metastatic status		Unknown
	M0	M1	
Denmark, 1997, 8/16 counties	12.3	22.0	17.1
Iceland, 1996–1998	62.9	23.3	26.6
Sweden, 1997			
Uppsala–Örebro	47.3	21.2	46.4
Västra	44.6	18.6	34.3

screening, and Swedish centres participated in the European Randomized Study on Prostate Cancer Screening, a screening programme has not been introduced.[16] Iceland has adopted a similar aggressive diagnostic strategy, as approximately half of Icelandic urologists receive their training in the United States of America (USA), where they may have been influenced in their attitude towards prostate cancer diagnosis and treatment; nevertheless, as in Sweden, no screening programme has been introduced.[17] The changes in incidence rates in the three countries are similar to those observed in Europe in general, reflecting more widespread use of PSA testing in screening or early case finding.[18]

The results of these different approaches are apparent in the incidence and mortality rates. Prostate cancer incidence in Sweden was significantly higher than in Denmark even before the introduction of PSA testing. The incidence increased rapidly in Iceland and Sweden from the 1990s and increased in Denmark 5–10 years later (Fig. 2). Relative survival evolved in the same way, while the mortality rates have been relatively constant.[1] These findings together strengthen the assumption that active case finding and consequently increased diagnosis of latent prostate cancer, while unlikely to be harmful in terms of loss of life expectancy, explain part of the improved survival and contribute to lead-time bias.[2,19,20] In the European Randomized Study, the lead time was estimated to be 6–12 years.[21] This possible effect of early case finding is supported by our finding that the age-standardised incidence rates of M0 prostate cancer are significantly lower in Denmark than in Iceland and Sweden (Table 5).

This study was based on selected cohorts of patients with newly diagnosed prostate cancer. The Danish patients lived in eight of the 16 counties, representing about 60% of the Danish population. All Icelandic cases diagnosed in 1996–1998 were included, and Swedish patients were identified in two population-based regional prostate cancer registers representing about 50% of newly diagnosed cases in 1997. The study thus included only a sample of all cases diagnosed; however, the survival of patients in each country resembled that in a Nordic study covering the same calendar period, indicating that the cohorts were representative.[1] As different grading systems are used routinely in the three countries and histological data were missing for a large proportion of cases, analyses with adjustment for histopathology could not be performed. Furthermore, information on PSA level at diagnosis was missing for a large number of patients, especially in Denmark. Both are important prognostic factors, and inclusion of this additional information might have changed our results.

Large differences in the distribution of clinical T stage, M status, differentiation of tumours and PSA level at diagnosis were found among the cohorts. Having metastatic disease at diagnosis increased the excess mortality rate 10-fold relative to M0, followed by hormone treatment, PSA level and clinical T stage. The effect of M status was similar in all three countries. The effect of clinical T stage >T2 was less pronounced in Danish patients than in Iceland and Sweden (results not shown). As therapy with curative intent was rarely offered in Denmark in the period of the study, this finding reflects less intensive staging.[22] Regardless of treatment, survival is closely associated with prognostic factors such as stage, histopathology and PSA level at diagnosis.[19,23–25]

Large differences in the use of therapy with curative intent were found. Although the percentage of patients offered curative therapy was lower than current standards, the proportion treated was similar to that in the Nordic countries in the period studied. Radical prostatectomy has been shown in a randomised trial to improve survival, as has PSA screening,[16,26] but the overall impact on survival was modest, and no differences in survival were found during the short follow-up.[26,27] No randomised study has been conducted to compare radiation therapy with observation and sur-

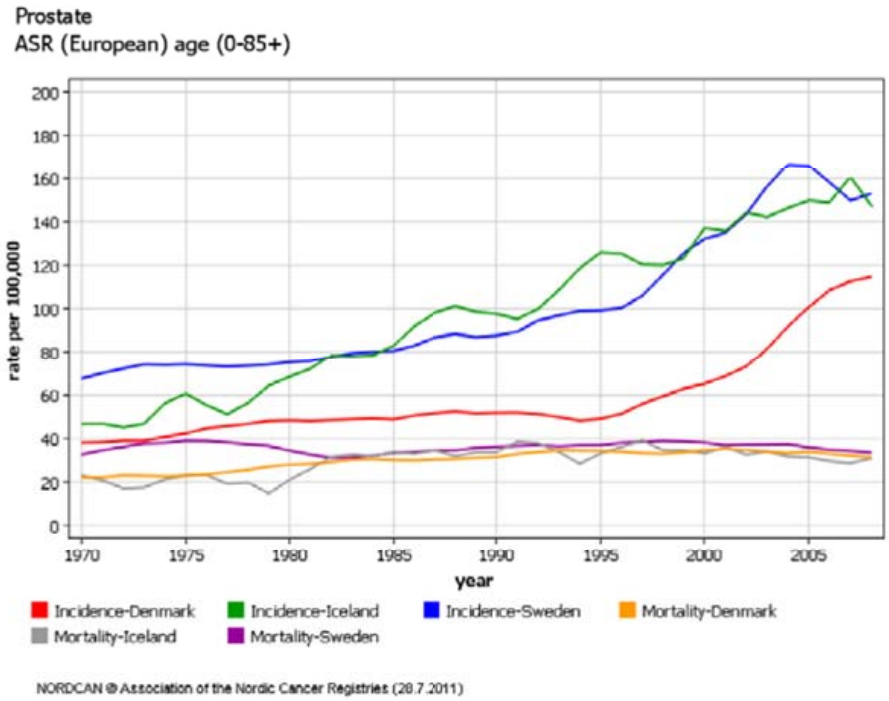

Fig. 2. Trends in age-standardised (European) prostate cancer incidence and mortality rates in Denmark, Iceland and Sweden.

gery; however, a study of patients with localised disease indicated that radiation was as effective as surgery.[28] In our study, excess mortality was significantly lower among patients managed curatively during a 5-year follow-up. As the results were similar in all countries, different use of therapy with curative intent is unlikely to explain the observed differences in excess mortality.

Hormone treatment within 6 months of diagnosis was associated with significantly higher excess mortality, perhaps because patients with metastatic disease are likely to receive hormone treatment early. Improved survival has been reported in patients with early prostate cancer and locally advanced disease, whereas no improvement was found for patients with clinically localised prostate cancer managed with anti-androgens.[29]

After stratification according to M status, the excess mortality in Danish M0 patients did not differ from that in similar Swedish patients. Therefore, the overall difference in RER between Denmark and Sweden was not due to differences in the management of M0 prostate cancer. Danish patients who were M+ had a significantly higher risk than Swedish patients. Stratification by M status did not change the results for Iceland relative to Sweden. As significantly more patients in both Iceland and Sweden were offered curative therapy, it is likely that some of those for whom curative therapy was proposed had minor metastatic lesions at diagnosis, shifting patients from M0 or MX to M+. Patients with asymptomatic metastatic prostate cancer are likely to have a better prognosis, which would thus reduce the excess mortality among M+ patients. Stage migration – the so-called 'Will Rogers phenomenon' – might thus have contributed to the difference in excess mortality after stratification for M status.[30]

The conclusion of the Nordic cancer survival study was that cancers at sites such as the prostate and breast, for which diagnostic procedures vary between countries, should be excluded from comparisons of survival from all cancers among countries because of the impact of early diagnosis on survival.[31]

Ultraviolet radiation has been proposed to have a possible protective effect, especially against high-grade prostate cancer[32]; however, differences in exposure to ultraviolet radiation are unlikely to explain the observed differences in mortality, given the relatively small geographical area studied. Table 3 shows higher excess mortality associated with a higher Gleason score in one analysis of Icelandic and Swedish data, and associated with more poorly differentiated WHO grade tumours in an analysis of Danish and Swedish data. Differences in diagnostic work-up may have influenced the results, as therapy with curative intent was used more frequently in Iceland and Sweden, suggesting that the patients were evaluated more intensively. As the patients were identified in population-based registries in the 1990s, the results may not be applicable to patients in situations with more intensive case finding.

The reporting of TNM stage to the Danish and Swedish Cancer Registers has been mandatory since 2004 and

2003, respectively, but the information has not yet been validated. Since 1998, the Icelandic Cancer Registry has requested physicians reporting patients with prostate cancer to also report the TNM stage; however, reporting is not mandatory and has not been validated. In this study, the clinical information was obtained from clinical databases, which are not necessarily nationally representative.

5. Conclusions

Comparison of relative survival from data in population-based cancer registers is an easy, feasible way to identify differences between countries, but register data have shortcomings. Comparisons of survival from prostate cancer are invalid unless adjustment is made for variation between countries in major prognostic factors. Most of the observed differences in 5- and 10-year relative survival in the Nordic countries reported for the period 1994–1998 were due to differences in clinical presentation at diagnosis. For international comparisons, information on prognostic factors like stage should be collected and adjusted for. Cancer registers and other national registers available for linkage should record such information. Alternatively, more effort should be made to validate mortality rates, which are less likely to be influenced by different diagnostic strategies. Unfortunately, the quality of registration of cause of death is less accurate than cancer registration, especially for the oldest population, who suffer from multiple chronic diseases. Nevertheless, comparisons based on mortality rates are likely to reflect real differences, unless there is systematic misclassification between countries.

Conflict of interest statement

None declared.

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Paper II

(i) Title page

Localized prostate cancer in two neighboring countries with different practices for early detection - A population based study

Short running title: Survival differences of localized disease

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(ii) Abstract

Objectives

Survival following a diagnosis of prostate cancer is lower in Denmark compared to the other Nordic countries. The aim was to elucidate possible differences in clinical presentation, diagnostics and survival of localized prostate cancer patients in Denmark and Iceland.

Methods

Follow-up was from diagnosis to the time of death, emigration, or end of study. Age-standardized relative survival was calculated by the observed divided by expected survival based on the country specific population mortality and age-standardized with the ICSS standard. Chi-square tests were used for homogeneity between countries in the distribution of clinical findings ($p<0.05$).

Results

LUTS were the predominant presentation. Diagnosis was mostly confirmed following TURP in Denmark and biopsies in Iceland. Icelandic patients were younger, underwent bone imaging more frequently, had lower PSA and well differentiated tumors were more common. A fivefold higher proportion of Icelandic patients were asymptomatic and diagnosed incidentally. Curative treatment was more commonly administered and endocrine therapy was introduced earlier in Iceland. M0 patients had comparable outcomes during the first four years following diagnosis, thereafter survival of Danish patients was significantly poorer. A significant difference in survival of MX patients was apparent during the whole follow-up period.

Conclusion

Lead-time bias is present as patients are diagnosed at different progress of their disease. Further limitations can include information bias, where cases could either be asymptomatic (PSA testing) or symptomatic. Administration of curative treatment, and perhaps earlier implementation of endocrine therapy, may have contributed to better relative survival in Iceland throughout ten years of follow-up.

(iii) Keywords

localized, prostate cancer, PSA, staging, survival.

(iv) Original article

INTRODUCTION

Similar to most Western countries the incidence of prostate cancer has risen dramatically in Iceland over the last three decades (Figure 1).[1,2,3] Danish physicians have had a more conservative approach towards diagnosis of prostate cancer among asymptomatic men[4]. This has resulted in fewer diagnosed cases and a delayed rise in incidence was seen in Denmark from around 1995 (Figure 1)[1,4,5]. In the study period, around 1997, prostate cancer was the most common cancer among men in Iceland and the third most common in Denmark.[6]

According to previous analyses, prostate cancer survival was significantly lower in Denmark than in the other Nordic countries[1]. The main objective of this study was to identify possible differences in the clinical presentation, diagnostics and survival of patients with clinically localized prostate cancer.

METHODS

Study population

The study population consisted of 950 patients from Denmark and Iceland described in detail in an earlier publication.[7] The Danish cohort consisted of 60% of all prostate cancer patients reported to the Danish Cancer Registry during the last 8 months of 1997. The Icelandic cohort consisted of all patients diagnosed in the 3-year period from 1996 to 1998 identified in the Icelandic Cancer Registry. Medical records were obtained and information on clinical findings was collected using a predesigned questionnaire (see appendix). Cases detected at autopsy or only mentioned on a death certificate were excluded from the analyses, as were patients with locally advanced (stage T3 and T4) and metastatic prostate cancer at diagnosis.

Variables used in the analysis

Clinical information obtained was used to determine TNM stage according to the classification of the International Union Against Cancer (UICC) 2002.[8] The classification for all cases was carried out by the same physician.

Metastatic status was classified as no metastasis found at diagnostic work-up (M0) or metastatic work-up had not been performed (MX). Patients without lymph node involvement (N0) had no spread of malignancy to lymph nodes following lymph node dissection.

Pretreatment PSA values were registered. Histopathological grade according to either WHO-criteria[9] or Gleason score[10] was recorded. The date of diagnosis was obtained from hospital records and cancer registries. Information on time of death was retrieved from the national population registers.

All citizens of Iceland and Denmark have a unique 10-digit civil registration number. By means of the civil registration number all cases of both cohorts were linked to the Civil Registration System in their respective country, which contain information on date of death, emigration and residence of all citizens. Thus, follow-up to death or emigration is reliable.

The nature of the first contact with the health care system was classified as lower urinary tract symptoms, asymptomatic (incidental finding of elevated PSA) or other symptoms. Method of diagnosis was classified as: no histological verification (most commonly due to comorbidity or old age), fine-needle aspiration biopsy, Trucut biopsy, transurethral resection of prostate (TURP) or transvesical prostatectomy (TVP). The date of initiation and type of endocrine treatment was recorded. Curative treatment included radical prostatectomy, external radiotherapy or brachytherapy.

Outcome assessment and statistical analysis

Patients were followed-up to the time of death, emigration, or to the end of study (December 31st 2008), whichever came first. Chi-square tests were used to test for homogeneity in the distribution of clinical findings between countries, a p-value of less than 0.05 was considered statistically significant. Relative survival was estimated as the ratio of the observed survival of men diagnosed with prostate cancer relative to the expected survival if the men diagnosed with prostate cancer had been subject to the background mortality in the general population. Age-standardization used was according to the International Cancer Survival Standard as described in the Nordic Cancer Survival Study.[11] Expected survival was estimated using national population mortality among men by one-year age and calendar periods using the Ederer 2 method. [11]

RESULTS

The study-population consisted of 443 patients with clinically localized (T1-2, N0/NX and M0/MX) prostate cancer, Table 1. Baseline characteristics are shown in Table 2. The mean age at diagnosis of prostate cancer was significantly higher in Denmark. Lower urinary tract symptoms were predominant in both populations. The percentage of Icelandic patients diagnosed following an incidental PSA test was five-fold higher than in Denmark. Most Danish patients (62.7%) were diagnosed following TURP, while a similar proportion of Icelandic patients (60.8%) were diagnosed by means of Trucut biopsies. Significantly more Icelandic patients had clinical stage T1c, whereas the proportion of patients with T2 disease was significantly higher in Denmark, Table 2.

Danish patients had higher PSA values (statistically significant) and a higher proportion had no pre-diagnostic PSA value. The proportion of patients with a PSA level above 100 ng/ml was more than twice as high in Denmark (16%) as in Iceland (7%). The majority of Danish patients had a tumor graded by the WHO grading system. The largest group of Danish cases had well differentiated disease (30%), while 19% had moderate and 16% poorly differentiated disease. Almost all Icelandic cases had a tumor graded by the Gleason score; most had well differentiated disease reflected by the fact that 58% had a low Gleason score (≤ 5), 30% had moderately differentiated disease (Gleason score 6-7) and only 8% had a poorly differentiated disease (Gleason score ≥ 8).

Diagnosis without histological verification was more common in Denmark and this subgroup in Denmark was significantly older than the rest of the Danish cohort (data not shown). In both

countries lymph node staging was rarely performed. Work-up for distant metastases was carried out significantly more often in Iceland (Table 2).

The number of patients receiving curatively intended therapy was significantly higher in Iceland. Endocrine therapy was introduced earlier in Iceland, but at the end of follow-up a larger proportion of Danish patients (58% in Denmark vs. 44% in Iceland) had been treated (Table 2).

Overall survival of men diagnosed with prostate cancer in Iceland was significantly higher than of their Danish counterparts. At the end of follow-up 54% of Icelandic men and 25% of Danish men were alive (not shown). Figure 2 shows the cumulated relative survival in the two countries ($p<0.001$ at 10 years after diagnosis).

The data were stratified according to metastatic work-up, i.e. for M0 and MX patients. Metastatic work-up was performed significantly more frequently in Iceland (64.6%) as compared to Denmark (41.3%). Patients with localized T1-T2 prostate cancer that underwent metastatic work-up had a tendency towards being younger than those with stage MX. No significant age difference between the two countries was found for M0 patients (Table 2).

No differences in pre-treatment PSA were present for M0 patients (Table 2) while differences persisted among those with MX disease (Table 3). A similar pattern in mode of detection and nature of first contact for all patients prevailed for the M0 group. Endocrine therapy was used less commonly among the men diagnosed with M0 disease. No significant difference in relative survival was observed between the Icelandic and Danish men diagnosed with M0 disease during the first 4 years of follow-up. After 5 years relative survival for Icelandic M0 patients was fairly constant but decreased sharply in Denmark (Figure 3a). The 10-year relative survival for men in Iceland diagnosed with MX disease was significantly higher compared to their Danish counterparts (Figure 3b).

DISCUSSION

Overall, relative survival of Icelandic men diagnosed with localized prostate cancer was significantly higher than that of their Danish counterparts. The Icelandic cases tended to be younger and compared to the Danish cohort a fivefold higher proportion of them were diagnosed following a PSA test. More Danish patients underwent surgery for bladder outlet obstruction prior to diagnosis, whereas Icelandic patients had biopsies performed. This suggests that many asymptomatic middle-aged men in Iceland may have been diagnosed with prostate cancer as a consequence of increased awareness and

opportunistic diagnostic activity.

The increase in prostate cancer incidence in Iceland began around 1973[6] (Figure 1), consistent with the implementation of TURP procedures.[12] A similar but weaker trend was observed in Denmark.[6] In both countries the number of operations decreased from the early 1990s as medical treatments for benign prostate hyperplasia were implemented.[12,13] Nevertheless the rise in prostate cancer incidence continued in Iceland, especially from around 1988-1990 and in Denmark from around 1995, respectively (Figure 1).[6] During the 1990s the incidence of prostate cancer has uniformly increased in the majority of European countries and incidence rates in Iceland and Sweden were among the highest in Europe.[14]

The discrepancy of prostate cancer incidence between Denmark and Iceland around 1990 may be explained by disparate urological practices and different attitudes towards PSA testing. At this period in time all Icelandic urologists completed their specialist training either in the United States or in Sweden, where a more aggressive approach towards early case finding has been practiced. The continued and sharper rise in incidence was consistent with a rapid rise in PSA testing in Iceland.[15] A more conservative approach towards early PSA-driven case finding was initially advocated in Denmark.[16,17] This attitude has, despite the recommendation not to use PSA testing as a screening tool, gradually changed since 1995.[18] The number of men being PSA tested in both countries increased.[15,19] A two to three-fold increase in the number of biopsies was observed in Iceland in the time period 1983-2003.[20] In 2006 incidence reached a peak in Iceland and has since been falling. In Denmark the incidence reached a plateau between 2010 and 2012.[6]

Meyer at al.[21]suggested that the true incidence rate of lethal prostate cancer in the Nordic countries remained unchanged from 1965-2006 where the difference in incidence was a consequence of differences in diagnostic intensity and thus also due to over-diagnosis of nonlethal prostate cancer.[21-23] The subsequent fall in incidence might be a consequence of first time testing, which has been shown to have a profound effect on incidence despite overall increased testing rates[24] and perhaps a declining interest in case finding[25] has played a role. Moreover, as autopsy procedures have generally been declining in most Western countries, it is possible that some prostate cancer cases have remained undiagnosed.

Previous publications, based on cancer registry data, have demonstrated lower survival of men

diagnosed with prostate cancer in Denmark compared to the other Nordic countries.[1] Restricting analysis to cases with clinical localized prostate cancer, we found that the Icelandic cohort still had a survival advantage compared to the Danish cohort.

Our study shows that a higher proportion of Icelandic men underwent work-up with bone imaging. This finding is consistent with a different approach towards curative therapy. When analyses were stratified according to M-stage, patients with M0 had comparable outcomes in the two countries during the first 4 years following diagnosis (Figure 3a). This may be explained by a smaller tumor burden in the Icelandic patients as they were subjected to more active case finding and the result could reflect lead-time bias. Furthermore, the Icelandic patients were more frequently offered curative therapy and the earlier introduction of endocrine treatment in Iceland may have been beneficial for the Icelandic cohort.

Lead time bias can, according to The European Randomized Study of Screening for Prostate Cancer (ERSPC), be estimated to 6-12 years.[26] The SPCG-4 study demonstrated a survival benefit in younger patients (< 65 years) managed with curative intend compared to watchful waiting.[27,28] The practice of radical surgery in Iceland may have improved survival and reduced mortality for some younger prostate cancer patients. In Iceland the survival of men diagnosed with MX disease was significantly higher than in Denmark. This may be related to the considerably larger proportion of their Danish counterparts having significantly higher PSA levels, thus likely reflecting greater tumor burden at the time of diagnosis.

In the 1980s, through the mid-1990s and even to this day age-standardized prostate cancer mortality rates in all the Nordic countries have remained fairly similar.[6] In the mid-1990s mortality rates increased slightly but thereafter began to fall in the Nordic countries as well as in higher-resource countries in Western Europe.[14]

Curative intended therapy in the Nordic countries was not fully implemented in the late 1980s and was adopted later in Denmark than the other Nordic countries.[22] Therefore, a rise in mortality rates in all the Nordic countries in the early 1990s may reflect higher rates of clinically symptomatic disease. According to Bray *et al.* little association between the rise in incidence in the late 1990s and the recent reduction in mortality has been found.[14]

The original cohorts in this study, prior to exclusion of patients with locally advanced and disseminated disease, showed that the percentage of patients with disseminated disease was twice as

high in the Danish cohort compared to the Icelandic cohort.[7] By analyzing the survival curves of the M0 and MX groups separately a clear discrepancy can be detected. Patients with stage MX contribute the most to poor survival in the first five years of follow-up (Figure 3a and 3b).

The strength of this study is that it is carried out in two Western countries with similar health-care systems based on equal access. The difference between the countries studied is in the strategy towards early case finding although health authorities in both countries have throughout the years and to this day not recommended PSA screening of asymptomatic men.[29,30] In Denmark the consensus towards diagnosis and attempted curative treatment was more conservative. However, practices in Iceland resembled concurrent clinical approaches in the United States and Sweden, with PSA driven case-finding to identify patients with the disease at its early stages that was eligible for curative treatment.

All cases were recruited by being reported to the cancer registry in their respective country, making selection bias negligible. Furthermore follow-up is complete, and all medical data in this study were retrieved and recorded by the same physician using a predefined questionnaire. Limitations include the retrospective nature of the study and lead-time bias.

CONCLUSION

Among patients with localized prostate cancer in two Nordic countries that are relatively homogenous in respect to standard of living, ethnicity and environmental risk factors, different approaches towards active case finding, presentation at diagnosis and management resulted in differences in survival. As a consequence of incomplete metastatic work-up of patients believed to have localized disease at the time of diagnosis, a high proportion is assigned stage MX. Lead-time bias has portrayed Denmark as having poorer survival while comparison of patients with a confirmed M0 stage shows no significant difference in survival during the first four years of follow-up. Lead-time bias, more frequent use of therapy with curative intent, and earlier implementation of endocrine therapy, may all have contributed to a better relative survival in Iceland throughout ten years of follow-up.

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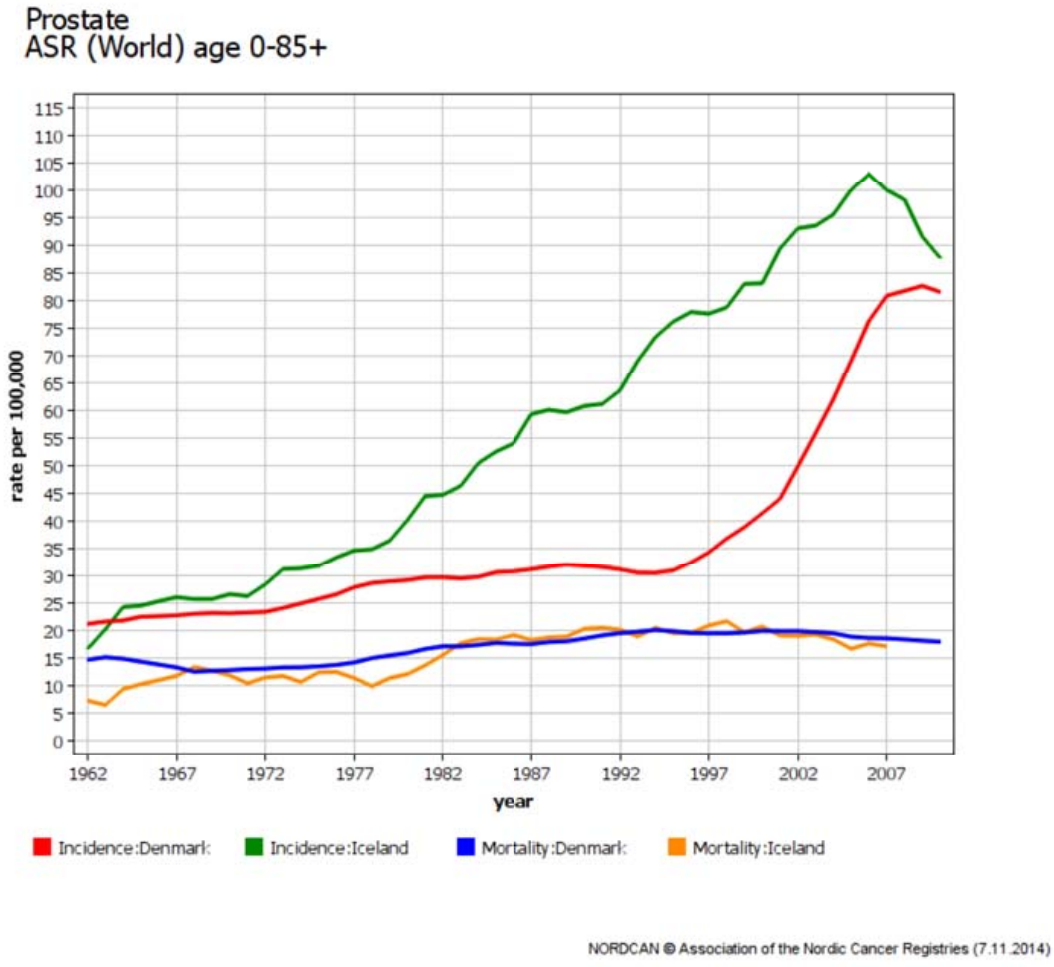

Figure 1.Trends in age-standardized prostate cancer incidence and mortality in Denmark and Iceland.

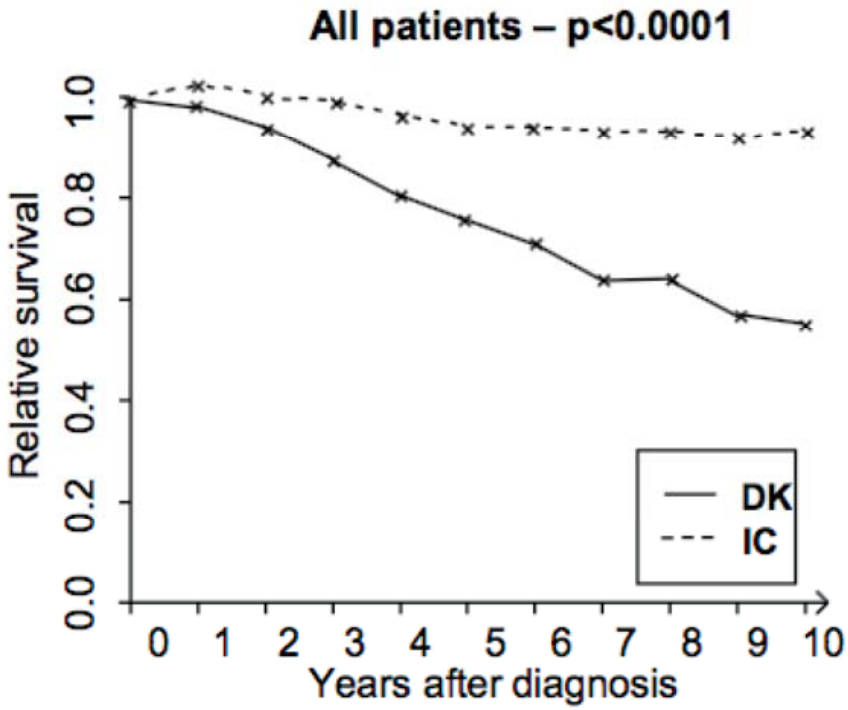

fig 2
Relative survival of men diagnosed with prostate cancer in and around 1997 in Denmark and Iceland during ten years of follow-up.

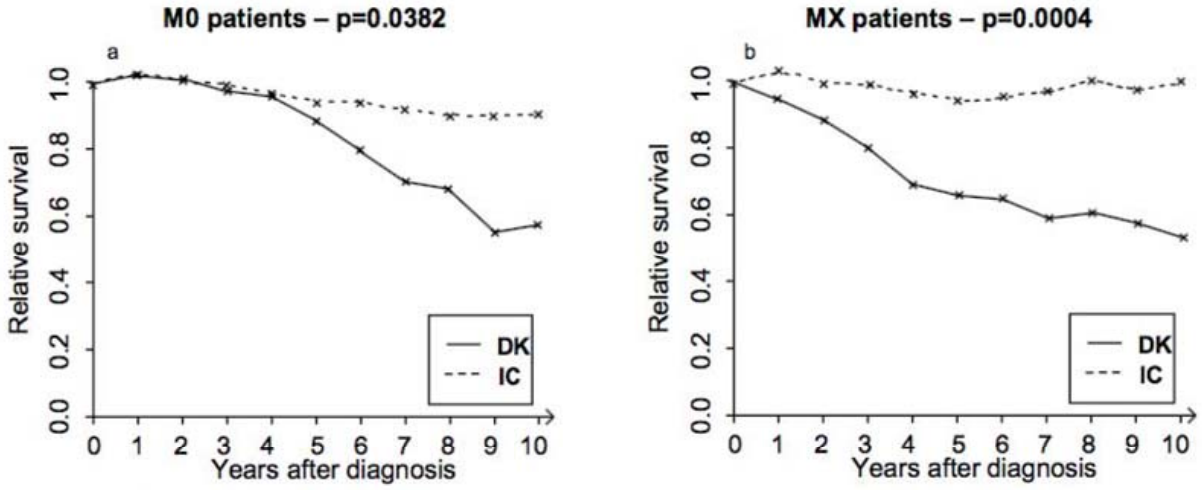

fig 3
Relative survival for Danish and Icelandi patients diagnosed in and around 1997 among M0 patients (3a) and MX patients (3b).

Table 1

Selection of a cohort of patients with localized prostate cancer (T1-T2 N0/NX M0/MX) younger than ninety years of age diagnosed in and around 1997 in Denmark and Iceland.

Distribution of inclusion and exclusion criteria	Denmark	Iceland
Prostate cancers in original cohort	**675**	**438**
Exclusions based on register information		
Incidental finding at autopsy or death certificate only	18	12
Previous or simultaneous diagnosis of another type of cancer	72	38
Not registered at time of cohort definition	10	-
Hospital records studied	**575**	**388**
Exclusions based on hospital records / clinical register		
Hospital diagnosis more than two years before diagnosis in CR	4	-
Diagnosis altered after pathological revision	2	1
Incidental finding at autopsy	1	-
Previous or simultaneous diagnosis of another type of cancer	-	2
No hospital records	3	-
Age 90 and above	16	11
Stage M+	234	75
Stage N+	4	17
Stage T3 or T4	71	43
Missing T-stage and TX	34	2
Patients included in the study	**206**	**237**

Table 2

Baseline characteristics of 443 men diagnosed with localized prostate cancer in and around 1997 in 8/16 counties in Denmark and all of Iceland.

Characteristics of the Study Cohort	Denmark all (n=206)	%	Iceland all (n=237)	%	p value*	Denmark M0 (n=85)	%	Iceland M0 (n=153)	%	p value*
Age, mean (sd)	74,7	7,6	72,7	8	0,001	72,9	7,7	71,1	7,9	0,089
Nature of first contact					< 0.001					0,023
Lower urinary tract symptoms (LUTS)	173	84	187	79		72	84,7	114	74,5	
Consequence of incidental PSA testing	5	2,4	29	12		2	2,4	20	13,1	
Other symptoms than LUTS	28	13,6	21	8,9		11	12,9	19	12,4	
Mode of detection					< 0.001					< 0.001
No histology	22	10,7	3	1,3		8	9,4	1	0,7	
Fine needle biopsy (FNA)	1	0,5	1	0,4		0	0	1	0,7	
Needle-biopsy (TRU-cut)	54	26,2	144	61		34	40	111	72,6	
Transurethral resection (TURP) or TVP	129	62,7	89	38		43	50,6	40	26,1	
Clinical stage					< 0.001					0,005
T1a or T1b	66	31	63	27		26	30,6	23	15	
T1c	7	4,4	37	16		5	5,9	23	15	
T2	133	64,6	137	58		54	63,5	107	69,9	
Pretreatment PSA value (ng/ml)					< 0.001					0,225
Normal (0-3.9)	15	7,3	30	13		9	10,6	11	7,2	
4-9.9	23	11,2	60	25		14	16,5	40	26,1	
10-99.9	104	50,5	116	49		45	52,9	88	57,5	
> 100	33	16	17	7,2		10	11,8	11	7,2	
Result unknown or not performed	31	15	14	5,9		7	8,3	3	2	
Histological grading										
Gleason score										
Gleason score 2-5	18	8,7	137	58		4	4,7	78	51	
Gleason score 6-7	23	11,2	70	30		6	7,1	52	34	
Gleason score 8-10	20	9,7	18	7,6		7	8,2	16	10,5	
Unknown	145	70,4	12	5,1		68	80	7	4,6	
WHO-criteria										
Well-differentiated	61	29,6	7	3		30	35,3	5	3,3	
Moderately-differentiated	39	18,9	1	0,4		18	21,2	1	0,7	
Poorly-differentiated	31	15,1	0	0		13	15,3	0	0	
Unknown	75	36,4	229	97		24	28,2	147	96,1	
N-stage					0,104					0,227
N0	5	2,4	13	5,5		4	4,7	13	8,5	
NX	201	97,6	224	95		81	95,3	140	91,5	
M-stage					< 0.001					
M0	85	41,3	153	65						
MX	121	58,8	84	35						
Curative intended therapy										
Radical prostatectomy	5	2,4	39	17		4	4,7	37	24,2	
Curative radiotherapy	1	0,5	14	5,9		0	0	14	9,2	
No curative treatment	200	97,1	184	78		81	95,3	102	66,7	
Endocrine therapy					< 0.001					0,001
Within three months after diagnosis	31	15,1	57	24		15	17,7	40	26,1	
More than three months after diagnosis	89	43,2	48	20		40	47,1	37	24,2	
No hormonal treatment	86	41,8	132	56		30	35,3	76	49,7	
TURP after diagnosis	61	29,6	36	15	< 0.001	35	41,2	23	15	< 0.001

* Chi-square tests have been performed for all categorical variables and t-test for age

Table 3

Pre-treatment PSA levels for Danish and Icelandic prostate cancer patients diagnosed with MX disease diagnosed in and around 1997.

PSA (ng/ml)	Denmark MX (%)	Iceland MX (%)	p value*
0-3.9	6 (5.0)	19 (22.6)	< 0.001
4-9.9	9 (7.4)	20 (23.8)	
10-99.9	59 (48.8)	28 (33.3)	
>100	23 (19.0)	6 (7.1)	
Unknown	24 (19.8)	11 (13.1)	

* Chi-square tests have been performed for categorical variables.

Paper III

VIDENSKAB OG PRAKSIS | ORIGINAL MEDDELELSE

Prostatacancer i Danmark 1943-2002

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Resume

Introduktion: Incidensen af prostatacancer (PC) er stigende. Tidligere opgørelser over udviklingen i Danmark har ikke kunnet påvise, at dette skyldes ændret diagnostisk aktivitet. I denne undersøgelse gennemgås udviklingen i incidens og mortalitet af PC i perioden 1943-2002 med fokus på de seneste ti år.

Materiale og metoder: Der blev foretaget en registerbaseret undersøgelse.

Resultater: Den aldersstandardiserede (World Standard Population) incidensrate af PC i Danmark er steget fra 11,4/100.000 i perioden 1943-1947 til 38,2/100.000 i perioden 1998-2002. Den tilsvarende mortalitetsrate er steget fra 13,5/100.000 i 1953 til 19,1/100.000 i perioden 1993-1997. Fra 1943 til 1992 var der ikke tegn på, at ændrede diagnostiske procedurer kunne forklare den stigende incidens. Fra 1993 og frem ses en acceleration i incidensen af PC. I samme periode er der i aldersfordeling og klinisk stadie hos de yngste patienter tegn på, at der er tale om en screeningsinduceret øgning af antallet af nyanmeldte PC-tilfælde.

Diskussion: I overensstemmelse med internationale undersøgelser fandt vi en stigende PC-incidens. I de seneste ti år har der været tegn på, at stigningen skyldes en øget diagnostisk aktivitet, formentlig primært som en usystematisk prostataspecifik antigenbaseret »gråzone«-screening. Denne udvikling er sket til trods for rekommandationerne om screening for PC og vil betyde et øget behov for udredning, behandling og kontrol af det stigende antal, specielt yngre, patienter med PC.

Prostatacancer (PC) er en hyppigt forekommende kræftform blandt specielt ældre mænd, og PC er i visse lande den hyppigst forekommende cancer blandt mænd. Incidensen af PC udviser store internationale udsving med de højeste incidensrater i USA og Nord- og Vesteuropa, mens incidensen i Asien er lav [1]. Flere undersøgelser har vist, at incidensen af PC er stigende i en lang række lande [1]. En del af denne stigning kan tilskrives en øget diagnostisk aktivitet, herunder screening baseret på måling af prostataspecifikt antigen (PSA); men flere resultater peger også på, at der herudover er en reel incidensstigning, der ikke kan forklares ud fra ændrede diagnostiske procedurer. Formålet med nærværende artikel er at gennemgå udviklingen i incidens og mortalitet af PC i Danmark over en 60-årig periode med særligt fokus på ændringerne i den seneste tiårsperiode, hvor kurativ behandling har været tilbudt, og PSA-baseret diagnostik formentlig har været anvendt i stigende omfang.

Materiale og metoder

Cancerregisteret (CR) har siden 1943 modtaget indberetninger om nydiagnosticerede kræfttilfælde fra kliniske afdelinger og patologiske institutter. Registeret er landsdækkende og anses for at være næsten komplet [2]. I CR blev nyanmeldte kræfttilfælde i perioden 1943-1977 kodet på basis af en modificeret udgave af International Classification of Diseases (ICD)-7; fra 1978 anvendes International Classification of Diseases in Oncology (ICD-O) [2] med samtidig konvertering af koderne til ICD-7.

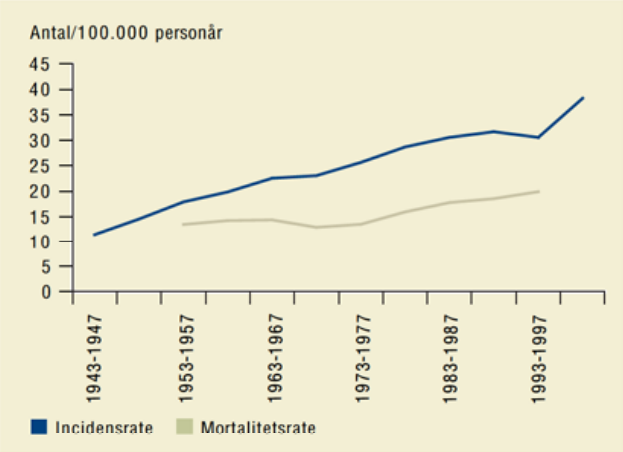
Opgørelsen er baseret på et udtræk fra CR fra perioden 1943-2002. På grund af manglende samkørsel med Dødsårsagsregisteret anvendes de foreløbige tal fra Cancerregisteret for årene 2000-2002. Data om PC-tilfælde baseret alene på oplysninger fra dødsattester er derfor ikke inkluderet for tre af årene i den sidst opgjorte femårsperiode. Antallet af nydiagnosticerede tilfælde i den seneste femårsperiode er således underestimeret ifølge Sundhedsstyrelsens estimater med ca. 40 tilfælde pr. år [3]. Foruden information om diagnosetidspunkt og alder ved diagnose, indeholder Cancerregisteret oplysninger om klinisk udbredelse, klassificeret som lokaliseret, regionalt avanceret, metastatisk eller uoplyst på diagnosetidspunktet.

Mortalitetsrater er beregnet på baggrund af oplysninger fra Dødsårsagsregisteret. Dette register blev oprettet i 1943, men på grund af de anvendte klassifikationer kan PC som dødsårsag først opgøres fra 1953. Da de årsagsspecifikke mortalitetsdata på opgørelsestidspunktet ikke var tilgængelige for årene 2001-2002, er mortalitetsraten for perioden 1998-2002 ikke udregnet. Aldersstandardiserede incidens- og mortalitetsrater er beregnet på baggrund af World Standard Population og opgjort for femårsperioder. Aldersspecifikke incidensrater er inddelt i femårsaldersgrupper efter det 50. år, og udviklingen er endvidere stratificeret efter alder ved diagnose og opgjort for personer henholdsvis < 70 år og ≥ 70 år. Oplysninger om befolkningsstørrelsen er indhentet fra Danmarks Statistik.

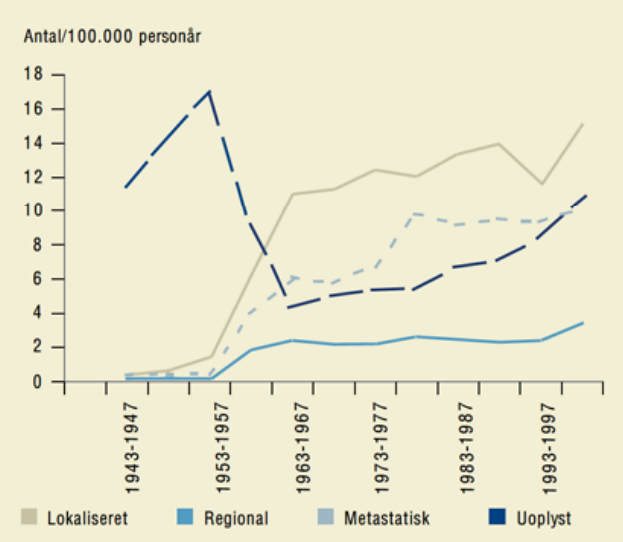
Ændringer i incidens- og mortalitetsrater er testet ved brug af lineær regression, og ændringer i de kliniske stadier er vurderet med χ^2-test for trend [4]. p-værdier < 0,05 er anset for at være signifikante.

Resultater

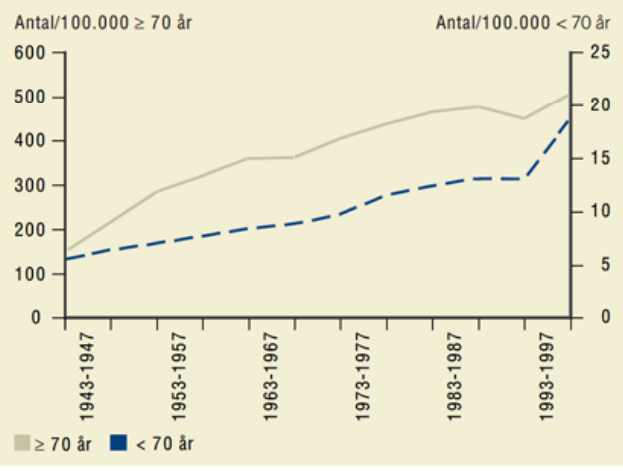
I perioden 1943-2002 blev der i alt anmeldt 60.654 tilfælde af PC til CR, stigende fra 1.310 anmeldte tilfælde i den første femårsperiode til 9.242 tilfælde i perioden 1998-2002. Udviklingen i aldersstandardiserede incidens- og mortalitetsrater ses i **Figur 1**. I observationsperioden steg PC-incidensen fra 11,4/100.000 i 1943-1947 til 38,2/100.000 i perioden 1998-2002, $r^2 = 0,97$, $p < 0,05$. Mortalitetsraten steg fra 13,5/100.000 i begyndelsen af 1950'erne til 19,1/100.000 i 1993-1997, $r^2 = 0,84$,



Figur 1. Aldersstandardiseret (World Standard Population) prostatacancerincidens- og mortalitetsrate.



Figur 2. Udvikling i prostatacancerincidens efter stadie i perioden 1943-2002 (aldersstandardiseret, World Standard Population).



Figur 3. Udvikling i aldersspecifik prostatacancerincidens for hhv. < 70-årige og ≥ 70-årige (aldersstandardiseret, World Standard Population).

$p < 0,05$. Der har i perioden været en signifikant tendens til stigende gennemsnitsalder ved diagnose fra 70,2 år i perioden 1943-1947 til 74,2 år i perioden 1993-1997, $p < 0,05$, men i den sidst opgjorte femårsperiode, 1998-2002, var gennemsnitalderen ved diagnose faldet til 73 år.

For alle femårsaldersklasser var der en signifikant stigende PC-incidens over tid, men med en tendens til en lavere stigningstakt i de ældste aldersgrupper i de senest opgjorte femårsperioder.

Udviklingen i aldersstandardiseret incidens stratificeret i henhold til anmeldt stadie i perioden 1943-2002 ses i **Figur 2**. Af figuren fremgår det, at den indrapporterede information om PC-udbredelsen i begyndelsen af observationsperioden var meget mangelfuld, idet hovedparten af patienterne blev anmeldt uden oplysning om stadie. For alle stadier ses fra femårsperioden 1963-1967 en signifikant stigende incidens, $p < 0,05$. Siden femårsperioden 1963-1967 har den procentuelle andel af patienter anmeldt med klinisk lokaliseret PC været signifikant faldende, og samtidig har der været en signifikant stigning i andelen af patienter uden oplysning om stadie, $p < 0,05$.

Da der har været speciel fokus på yngre patienter som mulige kandidater til kurativt intenderet terapi [5], er udviklingen i aldersspecifik incidens for personer under 70 år af særlig interesse. **Figur 3** viser udviklingen i aldersspecifik incidens for henholdsvis patienter < 70 og ≥ 70 år. Figuren viser, at der er en betydelig stigning i incidensen af PC blandt patienter < 70 år. **Tabel 1** viser antallet af nyanmeldte PC-tilfælde i de seneste to femårsperioder efter klinisk stadie på diagnosetidspunktet. Tabellen viser, at den øgede forekomst af PC hos patienter < 70 år overvejende skyldes et stigende antal patienter med klinisk lokaliseret PC.

Diskussion

Udenlandske undersøgelser viser samstemmende, at PC-incidensen er stigende, og at dele af stigningen kan forklares ud fra en øget diagnostisk aktivitet i form af stigende antal transuretrale indgreb [6] og PSA-baseret screening [7]. Således steg den aldersstandardiserede incidensrate i USA med mere end 38% over en syvårig periode i forbindelse med en sådan øget aktivitet [8]. Efterfølgende er der rapporteret om faldende incidens dels som konsekvens af en forudgående screeningsinduceret diagnosticering af prævalent, men endnu ikke klinisk PC i de første screeningsrunder, dels som følge af en vigende interesse for screening [9].

Et screeningsprogram, der opfylder målet og kan detektere PC i en tidligere og dermed potentielt kurabel fase, vil ud over at medføre en incidensstigning resultere i, at flere yngre patienter vil blive diagnosticeret med tidlige stadier af PC. Hvor PC-screening har været anbefalet og anvendt, er der da også rapporteret om faldende alder ved diagnose, stigning i andelen af patienter med lokaliseret PC og tendens til gunstigere histologisk gradering [10].

De danske rekommandationer vedrørende PC-screening

Tabel 1. Antal og procentuel fordeling af nyanmeldte prostatacancertilfælde i henholdsvis perioden 1993-1997 og 1998-2002 fordelt efter stadie ved diagnose, lokaliseret, regionalt avanceret, metastatisk og uoplyst.

	Stadie				
	lokaliseret n (%)	regional n (%)	metastatisk n (%)	uoplyst n (%)	I alt
1993-1997					
Alder, år					
< 70.	729 (35)	167 (8)	664 (32)	520 (25)	2.080
≥ 70.	2.022 (38)	317 (6)	1.491 (28)	1.508 (28)	5.338
1998-2002					
Alder, år					
< 70.	1.400 (44)	334 (10)	747 (23)	700 (22)	3.181
≥ 70.	2.026 (33)	362 (6)	1.700 (28)	1.973 (33)	6.061

har i hele studieperioden været uændrede, idet PSA-baseret screening frarådes. Denne anbefaling står i et delvist modsætningsforhold til indførelsen af kurativt intenderet behandling, hvor en logisk konsekvens må forventes at være øget fokus på tidlig diagnostik.

PC-incidensen i Danmark er godt tredoblet i perioden 1943-2002. I en tidligere undersøgelse af incidensudviklingen i perioden 1943-1992 fandt man ikke nogen ændringer i aldersfordeling, klinisk stadie eller anvendelse af transuretral kirurgi, der kunne indikere, at den stigende PC-incidens primært skyldtes øget diagnostisk aktivitet [11].

Betragter man imidlertid udviklingen inden for det seneste årti, findes der et fald i alder ved diagnose. Dette fald er formentligt reelt, idet det beskedne antal tilfælde fra dødsattester alene, som mangler i nærværende opgørelse, næppe vil ændre alderssammensætningen væsentligt, om end disse patienter typisk er ældre end gennemsnitspatienten. Samtidig viser udviklingen i de seneste ti år en kraftig stigning i antallet af nyanmeldte tilfælde af lokaliseret PC hos patienter under 70 år (Tabel 1), mens antallet af patienter med regional spredning, metastatisk PC eller uoplyst stadie i samme aldersgruppe kun stiger lidt. Disse fund kunne tyde på, at der trods anbefalinger om det modsatte og i overensstemmelse med fornemmelsen på de afdelinger, hvor man varetager kurativt intenderet behandling, foregår en vis »gråzone«-screening. Denne antagelse understøttes af det forhold, at rutinemæssig måling af PSA indgår i rutineundersøgelsen af blodprøverne på visse afdelinger på f.eks. H:S Rigshospitalet, og at der f.eks. på Københavns Praktiserende Lægers Laboratorium er registreret en næsten seksdobling af antallet af PSA-målinger fra 1.631 i 1994 til 9.353 i 2002.

Den øgede aktivitet kan også aflæses i et stigende antal diagnostiske procedurer, således er antallet af transrektale ultralydskanninger med biopsi mere end tidoblet i perioden 1997-2003 [12].

Overraskende er det, at det trods den formodede stigende interesse for kurativt intenderet terapi, fortsat er næsten 25% af tilfældene med de yngre patienter, der indrapporteres med uoplyst klinisk stadie. Om dette skyldes mangelfuld indrapportering af opfølgning (senere oplysninger om korrekt stadie ved diagnose) på disse patienter, manglende udredning eller en ændret kodepraksis, kan ikke afgøres ud fra det foreliggende materiale.

Den foreliggende undersøgelse synes at bekræfte en udvikling i PC-incidensen, som tidligere er set i andre lande, specielt USA. Sammenlignes udviklingen i den danske aldersstandardiserede incidensrate med den tilsvarende udvikling i USA i perioden omkring indførelsen af PSA-baseret PC-screening, må en yderligere og endnu mere markant stigning i incidens forventes i Danmark. Dette vil føre til en endnu større stigning i PC-prævalensen, fordi stigningen i incidens domineres af patienter med tidlige cancere og forventet lang overlevelse. Prævalensen af PC er steget med 35% inden for de seneste fem år [13]. Udviklingen har i perioden 2000-2004 medført en stigning i forbruget af henholdsvis gonadotropinfrigørende hormonanaloger på knap 60% og en femdobling i forbruget af antiandrogener, begge dele beregnet som anbefalet daglig døgndosis [14].

Vi har tidligere forsøgt at estimere den fremtidige incidens af PC og vurdere det fremtidige behov for behandling af yngre patienter med klinisk lokaliseret PC [15]. Det blev anslået, at det fremtidige behov for kurativt intenderet kirurgi ville være 100-130 operationer årligt, hvis man fastholdt en øvre aldersgrænse for radikal prostatektomi på 65 år [15]. Øget diagnostisk aktivitet og et vist skred i aldersgrænsen har medført, at der nu opereres 2-3 gange flere end forudsagt. *Møller et al* [16] fremskrev i 2002 antallet af PC-tilfælde på baggrund af den hidtidige udvikling og forsøgte i beregningerne at korrigere for effekten af PSA-baseret PC-screening. Alligevel overstiger den nuværende incidens forfatternes prognoser med ca. 20%.

Stigningen i både incidens og behandlingsbehov er således stejlere end tidligere forudsagt, og denne udvikling vil have endog ganske betydelige konsekvenser for den fremtidige dimensionering af sundhedsvæsenets tilbud om udredning, behandling og kontrol af PC.

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Interessekonflikter: Ingen angivet

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Paper IV

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ORIGINAL ARTICLE

Quality assessment of prostate cancer reports to the Danish Cancer Registry

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ABSTRACT

Background. The Danish Cancer Registry (DCR) is the oldest nationwide population-based cancer registry in the Nordic countries. At the time of the study the DCR recorded date of diagnosis, tumor stage and initial treatment. The validity of the clinical information reported to the DCR has never been analyzed.

Material and methods. Patients diagnosed with prostate cancer from 1 May to 31 December 1997 and living in eight Danish counties were identified through the DCR. Clinical data was retrieved from hospital records where date of diagnosis, stage at diagnosis and treatment received were registered.

Results. The mean age at diagnosis was 74.6 years (s.d. 8.6 years). Diagnosis was verified histologically for 87% of cases. Overall 95% of the patients had a difference less than three months between the reported date of diagnosis and the date found in hospital records. Correction of dates of diagnosis had no impact on survival. Hospital records identified 86 patients with T1-2 disease without distant metastases (M0), but only 56 of these patients (65%) were reported to the DCR as having localized disease. According to hospital records a total of 242 patients were confirmed having distant metastases (M1) at diagnosis but only 139 of these cases (57%) were reported to the DCR as such. Considerable "over reporting" of curative treatment was observed.

Conclusion. The DCR has been shown to be reliable in terms of new cases being reported. For the majority of cases there were insignificant differences concerning the date of diagnosis. However, the DCR information on stage and treatment was found to be inaccurate. Since 2004 the DCR registration process, including staging according to the TNM classification, has been carried out electronically from several registers. Future comparison between cohorts of different time intervals or international comparison should be interpreted with caution when clinical information is included.

The Danish Cancer Registry (DCR), founded in May 1942, is the oldest nationwide population-based cancer registry in the Nordic countries. Initially the DCR published data every five years but has from 1978 onwards issued annual reports [1]. In the earlier years reporting was voluntary, but has been mandatory ever since 1987 [2]. In 2004 reporting to the DCR changed from manual filing (a paper notification form filled out manually by clinicians) to electronic filing by linking to data available in national electronic patient and pathology registers. Previous reports have found close to 100% coverage of incident cases in the Nordic registries, including the DCR [1,3]. The DCR is updated annually and includes quality control of diagnoses.

The DCR records both person and tumor characteristics. Baseline data, e.g. date of birth, sex and date of death or emigration, are registered. From 1978 to 2003 tumors were categorized according to International Classification of Diseases for Oncology (ICDO-1) and International Classification of Diseases (ICD-7) with topography and morphology, date and basis of diagnosis, as well as age and residence at the time of diagnosis [3]. From 2004 onwards tumors have been categorized by the ICD-10 and ICD0-3 classifications, but data dating as far back as 1978 has been recoded to fit with these classifications. The DCR further recorded tumor stage and until 2003 even crude information on primary treatment, i.e. treatment given within the first four months after cancer diagnosis [4].

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It has been estimated, that differences in survival of patients with newly diagnosed prostate cancer in the year 1997 in Denmark, Iceland, and Sweden to a large extent could be explained by differences in clinical stage at diagnosis [5]. The aim of the present study was to validate the information reported to the DCR on Danish prostate cancer patients diagnosed in 1997 by comparing it to data obtained from hospital records, including medical charts, pathology reports, and findings from diagnostic imaging procedures.

Material and methods

All prostate cancer patients diagnosed in between 1 May and 31 December 1997, living in eight of 16 Danish counties, were identified in the DCR. They represented five urban areas and three rural areas. Patients included in the study cohort had to have prostate cancer recorded as their first primary tumor in the DCR, disregarding non-melanoma skin cancer. Cases whose diagnosis of prostate cancer was first obtained at autopsy or only mentioned on a death certificate were excluded. Information on the date of diagnosis (recorded as month and year of the patient's first contact with the health care system), clinical stage (categorized as localized, regional, metastatic, or unknown), and treatment within the first four months were retrieved from the DCR. Treatment data on surgical intervention was categorized as diagnostic, palliative or radically attempted procedures. Other types of treatment recorded were radiation, chemotherapy, hormonal treatment, no treatment, and unknown/unstated.

Information from hospital records was collected using a predesigned questionnaire (Supplementary Appendix, available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1054948). Clinical TNM stage was determined according to the International Union Against Cancer (UICC) classification [6] from 2002 by evaluating tumor size, node involvement and metastases recorded in the hospital records.

The date of diagnosis from the hospital records was recorded as the date of histological verification or in some cases (those without histological verification) as the date of clinical diagnosis based on a high PSA level, imaging results (multiple x-ray or bone scan) and/or abnormal digital rectal exploration of the prostate.

Lymph node involvement (N1) was recorded only if either lymph node dissection or imaging showed lymph node involvement. Patients classified with N0 disease had no sign of malignancy following lymph node dissection. Patients were categorized as M1 if they had a positive bone scan and/or positive findings on x-rays of the skeletal system. Other distant metastases were recorded only had they been verified by histopathology or if diagnostic work-up showed metastasis, using either computed tomography (CT) scan or ultrasonography. Curatively intended treatment was recorded if the patient had undergone radical prostatectomy, external radiation therapy or brachytherapy.

In 1997 the DCR coded stage into four different groups (localized, regional, metastatic and unknown) as indicated by the clinician on the notification form. In order to compare the reported stage with clinical tumor stage from hospital records, we used cross-tables based on T- and M-stages, where we used T1-2 to represent localized, T3 for regional and T4 for disseminated disease. N-stage was registered for very few cases and hence not used here.

The time interval between the reported and the observed date of diagnosis was measured in months. Survival analysis was computed by means of the PROC LIFETEST procedure in SAS, which computes non-parametric tests to compare the survival curves of two or more groups. All patients were reported to have localized prostate cancer and survival was stratified according to M-stage.

Results

Between 1 May and 31 December a total of 575 patients, living in eight Danish counties, were diagnosed with prostate cancer as their first primary cancer and reported to the DCR. Hospital records could not be retrieved for three patients, one was only mentioned on a death certificate and two patients turned out not to have prostate cancer following pathological revision (Table I). Thus, 569 patients were included in the study. The mean age at diagnosis was 74.6 years (s.d. 8.6 years). Of these 494 patients (87%) had histologically verified prostate cancer, and in the remaining 75 patients (13%) diagnosis was based on clinical findings. Distribution of TNM-stages, pretreatment PSA-values from hospital records and stage registration from the DCR are shown in Table II.

The hospital date of diagnosis was most often the date when diagnosis was histologically verified, while the DCR-date was the date of first contact with the health care system. For 70% of cases there was no difference between the two dates and overall 543 (95%) of the patients had a difference less than three months. Only 10 patients had a difference exceeding one year (Table III). Correction of dates of diagnosis had no impact on survival (data not shown).

Thirty-three patients were reported to the DCR having undergone radical prostatectomy (RP). Two of these cases were confirmed in the hospital records

Table I. Inclusion and exclusion criteria in a population-based study cohort of patients with prostate cancer diagnosed between 1 May and 31 December 1997 in eight counties in Denmark.

Prostate cancers in cohort from the DCR database	675
Exclusions based on DCR data	
Incidental finding at autopsy or death certificate only	18
Previous or simultaneous other cancer diagnosis	72
Not in database at time of registration	10
Hospital records obtained	575
Exclusions based on hospital records	
Diagnosis altered after pathological revision	2
Incidental finding at autopsy	1
Previous or simultaneous other cancer diagnosis	3
Patients included	569

while 24 of the 33 cases were treated with transurethral resection of the prostate (TURP) within four months following diagnosis. According to hospital records additional five patients underwent curative surgery within the first four months following diagnosis, without being reported to the DCR. Curative radiotherapy (RT) was reported to the DCR in 16 cases, but based on hospital records only four patients had curative intended radiation therapy and only one was registered with RT in both sources (Table IV).

Hospital records identified 86 patients with T1-2 disease without distant metastases (M0), but only 56 of these patients (65%) were reported to the DCR

Table II. Distribution of clinical stage and PSA level at diagnosis from hospital records, and stage reported to the DCR of Danish prostate cancer patients diagnosed between 1 May and 31 December 1997 in eight counties in Denmark.

Baseline characteristics	No. of patients N = 569	Percent (%)
T stage		
T1	87	15
T2	232	41
T3	122	21
T4	60	11
TX	68	12
N-stage		
N0	10	2
N1	25	4
NX	534	94
M-stage		
M0	129	23
M1	242	43
MX	198	35
Pretreatment PSA value (ng/ml)		
0–3.9	19	3
4–9.9	27	5
10–49.9	129	23
50–99.9	82	14
>100	224	39
Not performed, unknown	88	15
Stage, DCR		
Localized	186	33
Regional	43	8
Metastatic	166	29
Unknown	174	31

Table III. Time difference between the reported date of diagnosis to the DCR and the date of diagnosis found in hospital records for Danish prostate cancer patients diagnosed between 1 May and 31 December 1997 in eight counties in Denmark.

Difference in dates	Hospital date before DCR date	DCR date before hospital date	Total
0 months	0	0	400
1–3 months	36	107	143
4–12 months	12	4	16
1 year +	7	3	10
Total	55	114	569

as having localized disease (Table V). According to hospital records a total of 242 patients were confirmed having distant metastases (M1) at diagnosis, irrespective of their T-stage, but only 139 of these cases (57%) were reported to the DCR as such (Tables IV and V). Hence, 103 cases were found to have distant metastases according to hospital records, but were not reported to the DCR (Table IV). Lymph-node staging was only rarely performed, and had to be left out in validating the quality due to limited cases.

Of the 569 cases reported to the DCR, 174 cases were reported having unknown stage (31%). In hospital records T-stage could not be determined (TX) for 68 patients; in this group nine had no distant metastases (M0), 32 had confirmed distant metastases (M1) and the remaining 27 had unknown dispersion (MX).

Cases with T1-2 tumor, that did not undergo further work-up and therefore had unknown dispersion (MX) were 128, or approximately 23% of all patients. Half of the 128 patients were reported to have localized disease to the DCR.

There was no statistically significant difference in the distribution of M-stage between patients with a date of diagnosis within or exceeding four months. Likewise, there was no significant difference in M-stage between rural and urban areas (data not shown).

Discussion

Previous studies have demonstrated that the DCR is nearly complete in terms of number of cases [7]. However, the validity of the clinical information gathered has never been analyzed. In our study we found a relatively small discrepancy between the date of diagnosis registered in the DCR and the one found in the hospital records. A total of 143 patients (25%) had a disparity of ± 3 months and only 5% of the patients had a difference exceeding four months between dates recorded. The difference in dates recorded may be a consequence of a delay in completing paperwork or a difference in definition of the date

Table IV. Comparison of the number of prostate cancer patients with reported and confirmed distant metastases at diagnosis and whether they received curative treatment.

	Hospital records	%	DCR	%	Matching cases*	%
M1	242	43	166	29	139	57
Radical prostatectomy (RP)	7	1	33	6	2	29
No radical prostatectomy	541	95	536	91	507	94
Unknown if radical prostatectomy	21	4	21	4	0	0
Radiation therapy (RT)	4	1	16	3	1	25
No radiation therapy	544	95	553	93	525	97
Unknown if radiation therapy	21	4	21	4	0	0

*Number of cases registered in both hospital records and DCR (per cent according to cases found in hospital records).

of diagnosis. The observed differences in date of diagnosis had negligible effect on overall survival. In the period studied, reporting relied on paper forms submitted to the DCR. Since 2004 the DCR registration has been electronic and linked to the National Patient Register, the National Pathology Register and the National Cause of Death Register [3]. Based on the finding that delayed reporting in the older version of the DCR had no impact on survival estimates, it is unlikely that future survival estimates will be affected by a change in the registration procedure.

The DCR recorded treatment within the first four months following diagnosis whereas this study had information on all types of treatment from the time of diagnosis and during more than 10 years of follow-up. Of the seven patients undergoing radical prostatectomy, four were operated on within four months of diagnosis while the remaining three patients had surgery between five and 18 months following diagnosis. Only one of the four patients undergoing RT was treated in the first four months, the remaining three between five months and five years following diagnosis. As the DCR only recorded treatment during a four-month long period following diagnosis, an underestimation of treatment administered is likely. During this period of time the patients may not have completed full preoperative assessment, may not have been able to make treatment decisions or may still have been receiving adjuvant hormonal therapy prior to being treated with curative intended procedures. Most patients with T1-2 prostate cancer did not undergo further work-up for distant metastases, i.e. 128 of 569 had stage MX. As 61 of the 128 patients were reported to have localized disease to the DCR, this can reflect a lack of interest for further work-up and illustrate the conservative approach, which was predominant in Denmark at the time of the study [8].

However, our findings demonstrated a considerable "over reporting" of curative treatment (Table IV). A possible error may have occurred when the physician ticked the box "operation" and did not state whether an operation was attempted to be radical, palliative or merely diagnostic. Further, it may be a consequence of a misunderstanding in the reporting procedure, i.e. registering palliative radiation therapy as curatively intended or TURP as radical surgery. The quality of reported treatments has not previously been systematically validated. Since 2004, information on administered treatment has not been registered in the DCR, but has thenceforward been available from the National Patient Register, which receives electronic notifications from clinical contacts, presumably making data more reliable.

Table V. Comparison of clinical stage in hospital records and stage in the Danish Cancer Register for Danish patients diagnosed between 1 May and 31 December 1997 in eight counties in Denmark.

HOSPITAL	RECORDS	DANISH CANCER REGISTRY (DCR)				
M-stage	T-stage	Unknown	Localized	Regional	Distant metastasis	Total
M0	T1-2	21	56	6	3	86
	T3	10	11	6	0	27
	T4	2	1	2	2	7
	TX	3	2	3	1	9
M1	T1-2	28	19	4	54	105
	T3	18	6	2	39	65
	T4	8	5	2	25	40
	TX	6	4	1	21	32
MX	T1-2	49	61	10	8	128
	T3	15	12	1	2	30
	T4	6	3	2	2	13
	TX	8	6	4	9	27
TOTAL		174	186	43	166	569

The validity of N-stage was not assessed due to a limited number of patients being evaluated. Patients with bone metastases at diagnosis were greatly underreported to the DCR. This demonstrates that a group of patients with distant metastases (M1) was not correctly reported to the DCR, and even a few patients with localized disease (T1-2M0) in hospital records were registered as having distant metastases in the DCR. These findings indicate that outcome studies stratified on stage based on cancer register data prior to the introduction of TNM in the cancer registry in 2004 should be interpreted with caution, even if adjustment for clinical and metastatic status at diagnosis has been carried out.

Some of the differences between hospital records and register-based information observed in this study may reflect different interpretations among clinicians of the reporting procedure to the DCR, both for the date of diagnosis and stage, and differences may be a consequence of insufficient ambition towards the reporting procedure. The study period, 1997, was chosen as the Nordic study was originally intended to be a part of the EUROCARE high-resolution study on prostate cancer, but was in the end not included due to a delay in the data collection. A modernization of the DCR was introduced in 2004 by the implementation of ICD-10, recoding of ICD-O-1 to ICD-O-3 back to 1978 and making reporting of the TNM status to the DCR at the time of diagnosis mandatory [3]. Whether the change in registration procedure has increased the validity of clinical information in the DCR has to be assessed. The cohort studied included all prostate cancer patients, living in eight counties who were diagnosed in the last eight months of 1997, comprising around 60% of the whole Danish population. The survival of the cohort closely resembled the survival reported on nationwide studies on cancer register data covering the same calendar period, indicating that the cohort was representative for all Danish incident prostate cancers [9]. Therefore, the results of this study presumably reflect the validity of clinical information in the DCR nationwide. The patient characteristics showed that more than 40% of the patients had metastatic disease according to hospital records, and the mean PSA value was high (Table II), underlining that the routine use of PSA measurements was less common in Denmark.

Valid and up-to-date data are essential for clinical quality monitoring and epidemiological research. International studies comparing outcome often rely on data from central registries.

The findings have two major implications. First, misclassifications of patients, especially underreporting of patients with metastatic disease, can seriously jeopardize international comparisons based on register data. Second, if accuracy in reporting tends to be more precise or change over time, historical data may be difficult to compare to more recent patient cohorts.

Previous register-based studies on prostate cancer in the Nordic countries have shown large differences in relative survival and excess mortality with a poorer outcome in Denmark [9]. The difference in excess mortality between Denmark and Sweden virtually disappeared when adjusting for metastatic status at diagnosis [5].

Conclusion

The DCR information on stage and treatment was found to be inaccurate. Although the DCR has been shown to be reliable in terms of new cases being reported, substantial differences were found when essential clinical parameters were studied comparing hospital records with register-based information. Since 2004 the DCR registration process has been carried out electronically from several registers. This includes electronic reports on cancer stage according to the TNM, but these records have not yet been validated. Given the inaccuracy on clinical information found in this study, future comparison between cohorts of different time intervals or international comparison should be interpreted with caution when clinical information is included.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Paper V

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Original Research

Improved survival for patients with *de novo* metastatic prostate cancer in the last 20 years

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Abstract ***Introduction:*** During recent years, several new life-prolonging therapeutic options have been introduced for patients with metastatic prostate cancer (mPCa). The aim of the present study was to evaluate the changes in the survival of patients diagnosed with mPCa prior to and in the early period of the implementation of these new agents.

Patients and methods: The study population consisted of 207 men diagnosed in 1997 and 316 men diagnosed in the period 2007–2013 with *de novo* mPCa and managed with initial endocrine therapy. Men were followed for overall survival and PCa-specific survival.

Results: At the time of diagnosis, men diagnosed in the period 2007–2013 had less comorbidity, lower prostrate-specific antigen levels and lower clinical tumour categories than men diagnosed in 1997. A significantly higher proportion of men diagnosed in 1997 were managed with surgical castration (57% versus 9%). Only one patient diagnosed in 1997 received second-line therapy compared with 81 men (26%) diagnosed in the period 2007–2013. The median overall survival was significantly longer for men diagnosed between 2007 and 2013 compared with men diagnosed in 1997 (39.4 months versus 24.2 months, $p < 0.0001$). Likewise, the cumulative incidence of PCa-specific death was higher among men diagnosed in 1997 compared with men diagnosed between 2007 and 2013, with 5-year cumulative incidences of 72% and 47%, respectively ($p < 0.0001$).

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Conclusion: Survival in men diagnosed with metastatic PCa has improved significantly over time. The improved survival can in part be explained by lead-time bias, but also by the introduction of new life-prolonging treatments.

1. Introduction

Prostate cancer (PCa) is androgen dependent, and endocrine therapy has been a cornerstone in the management of men with metastatic PCa since Huggins and Hodges described the benefits of androgen ablation nearly seven decades ago [1]. Most of the PCas do respond to endocrine therapies; however, most cancers acquire the capability to proliferate despite having reached castrate levels of serum testosterone, i.e. become castration resistant (CRPC) [2]. Until recently, endocrine therapies—either as castration-based androgen deprivation therapy (ADT), androgen receptor inhibitors, oestrogens or combinations thereof—were the only available treatment options for men with metastatic PCa. However, during the last decade, a number of therapies have demonstrated a survival benefit for CRPC patients in randomised controlled trials [3].

First, two taxan-based chemotherapies, docetaxel [4,5] and cabazitaxel [6], have been approved for men with symptomatic metastatic CRPC. Second, new androgen-targeting therapies, abiraterone acetate [7,8] and enzalutamide [9,10], were approved for men with metastatic CRPC both before and after chemotherapy. Most recently, radium-223 [11] has been approved in the clinical management of men with metastatic CRPC.

While each of these new therapies has demonstrated survival benefits in randomised clinical trials, less is known about their efficacy in unselected populations managed outside clinical trials. Furthermore, an increased awareness of the disease, even in a population where PCa screening is not recommended, may have affected survival in patients with mPCa due to lead-time bias, introducing an apparent survival benefit in patients within the same clinical category. To further elucidate the survival changes for men diagnosed with *de novo* mPCa before and after the implementation of the new life-prolonging treatments, we compared the survival between two cohorts of Danish men diagnosed with mPCa in two different time periods; a historical nation-wide cohort of men diagnosed in 1997 and a contemporary cohort of men diagnosed between 2007 and 2013.

2. Patients and methods

The study populations derive from two cohorts of men diagnosed with *de novo* mPCa who received endocrine therapy as the first-line treatment. The historical cohort consists of men diagnosed with *de novo* mPCa identified among all Danish men diagnosed with PCa in the last 8 months of 1997. As previously described in detail, all men were identified in the Danish Cancer Registry. The date of diagnosis and tumour characteristics, including the results from diagnostic workups, were retrieved from the Danish Cancer Registry and patient records [12]. A total of 35 men with mPCa were excluded from the original study population, as they did not receive immediate endocrine therapy.

The contemporary cohort consists of an unselected, consecutive series of men identified in the local pathology database. These men were diagnosed with *de novo* mPCa at the Department of Urology, Frederiksberg Hospital, Denmark between January 1st 2007 and December 31st 2013 [13]. The following diagnostic information was registered retrospectively from patient records: age, prostate-specific antigen (PSA) level, Charlson comorbidity index (CCI), clinical tumour category (cT), histological grade (World Health Organisation grade or Gleason score), distant metastasis and primary treatment. Subsequent life-prolonging therapies, vital status and cause of death were updated until December 31st 2014 and January 31st 2016 for the historical cohort and the contemporary cohort, respectively. The study was approved by the Danish Data Protection Agency (file no. 2011-41-7017) and by the Capital Region of Denmark (file no. 2012-58-0004).

2.1. Statistics

Differences in baseline characteristics between the cohorts were tested using the chi-squared-test for categorical variables and the Mann–Whitney *U* test for continuous variables. Kaplan–Meier survival analysis was used to estimate the overall survival and log-rank analysis was used to compare survival between the two cohorts. The cumulative incidences of PCa-specific death and other-cause mortality were analysed using the Aalen–Johansen method for competing risks. Non-PCa death was treated as a competing event when analysing the risk of PCa death and vice versa. Gray's test was used to assess differences in the cumulative incidence between the cohorts [14]. Cox regression analyses were used to estimate the risk of death for men with complete baseline information and included age (continuous), PSA (continuous), CCI (0, 1, ≥2), cT (cT1, cT2, cT3 and cT4) and primary treatments (GnRH agonists, orchiectomy, total androgen blockade, androgen receptor inhibitors and oestrogens). The results

are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). PSA was entered on the log scale base 2; consequently, HRs represent two-fold differences in PSA levels, whereas HRs represent 5-year differences for age. Both univariate and multivariable Cox regression analyses included only men with complete baseline information in terms of age, PSA, CCI, cT category and first-line treatment.

The 1-, 3- and 5-year relative survival was calculated. Relative survival is defined as the observed survival divided by the expected survival in the patient group. Follow-up for death was updated until December 31st 2014 and January 31st 2016 for the historical cohort and the contemporary cohort, respectively. The observed survival was estimated using the actuarial method and the expected survival by the Ederer II method [15]. The expected survival was estimated from the male population mortality rates stratified by age and calendar time in 1-year intervals. Relative survival can be interpreted as the survival if death only from the cancer was possible. Since the age-distribution of patients differs over time, 1-, 3- and 5-year relative survival figures were age-standardised with the International Cancer survival Standard, as used in the Nordic Cancer Survival Study [16]. For the contemporary cohort, not all patients could be followed for death up to 5 years and hence censored accordingly.

All tests were two-sided, and the significance level was set at $p < 0.05$. Statistical analysis was performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Baseline characteristics of the 207 men diagnosed in 1997 and the 316 men diagnosed in 2007–2013 are presented in Table 1. Men diagnosed in 1997 had a significantly higher PSA (median PSA: 258 ng/ml versus 158 ng/ml, $p < 0.0001$), a more advanced cT category ($p < 0.0001$), and a higher CCI ($p = 0.03$) at diagnosis than men diagnosed in the period 2007–2013. Furthermore, a difference in primary endocrine therapy was found, as 57% of the men diagnosed in 1997 underwent orchiectomy compared with only 9% of men diagnosed between 2007 and 2013, where GnRH agonists were almost exclusively used.

Life-prolonging therapies were administered in only one man (0.5%) from the historical cohort compared with 81 (25.6%) men from the contemporary cohort (Table 2). The most frequently used therapies were docetaxel and abiraterone acetate.

The overall survival differed significantly between the cohorts, with a median survival of 24.2 months (95% CI: 18.3–28.4) in the historical cohort compared with 39.4 months (95% CI: 31.2–46.0) in the contemporary cohort, $p < 0.0001$ (Fig. 1).

Table 1
Baseline characteristics.

Variables	1997 cohort	2007–2013 cohort	p Value[a]
	n = 207	n = 316	
Age at treatment start, years, median (IQR)	74 (68–79)	73 (67–80)	0.61
PSA at treatment start, ng/ml, median (IQR)	258 (83–726)	158 (48–391)	<0.0001
Charlson co-morbidity index, n (%)			0.03
0	86 (41.5%)	170 (53.8%)	
1	79 (38.2%)	91 (28.8%)	
≥2	38 (18.4%)	55 (17.4%)	
Unknown	4 (1.9%)	–	
Clinical tumour category, n (%)			<0.0001
cT1	12 (5.8%)	73 (23.1%)	
cT2	77 (37.2%)	116 (36.7%)	
cT3	63 (30.4%)	87 (27.5%)	
cT4	39 (18.8%)	27 (8.5%)	
Unknown	16 (7.7%)	13 (4.1%)	
Biopsy histopathology, n (%)			NA
WHO well-differentiated	6 (2.9%)	–	
WHO moderate-differentiated	50 (24.2%)	–	
WHO poor-differentiated	83 (40.1%)	–	
GS ≤ 7	–	61 (19.3%)	
GS 8	–	83 (26.2%)	
GS 9–10	–	148 (46.8%)	
Unknown	68 (32.9%)	24 (7.6%)	
Metastasis at diagnosis, n (%)			1.0
M1	207 (100%)	316 (100%)	
First-line treatment, n (%)			<0.0001
GnRH agonist	48 (23.2%)	281 (88.9%)	
Orchiectomy	118 (57.0%)	27 (8.5%)	
Total androgen blockade	24 (11.6%)	8 (2.5%)	
Androgen receptor inhibitor	15 (7.2%)	–	
Oestrogens	2 (1.0%)	–	

Abbreviations: GS = Gleason score; IQR = inter-quartile range; LHRH = luteinising hormone–releasing hormone; NA = not assigned; PSA = prostate-specific antigen.

[a] The p value represents the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables.

The cumulative incidence of PCa-specific mortality was also significantly higher for men diagnosed in 1997 compared with men diagnosed between 2007 and 2013, with 5-year cumulative incidences of PCa-specific mortality of 72.4% (95% CI: 66.3–78.5) and 47.2% (95% CI: 41.1–53.3), respectively, $p < 0.0001$ (Fig. 2). The median PCa-specific survival was 28.4 months (95% CI: 23.3–33.5) in the historical cohort compared with 68.6 months (95% CI: 55.6–87.7) in the contemporary cohort. In contrast, other-cause mortality remained virtually unchanged with 5-year cumulative incidences of 11.7% (95% CI: 7.3–16.1) and 20.4% (95% CI:

Table 2
Life-prolonging treatments.

Life-prolonging treatments	1997 cohort	2007–2013 cohort
	n = 207	n = 316
Life-prolonging treatments, n (%)		
Total number of patients	1 (0.5%)	81 (25.6%)
Specific life-prolonging treatments, n (%)		
Docetaxel	1 (0.5%)	52 (16.5%)
Cabazitaxel	–	20 (6.3%)
Abiraterone acetate	–	51 (16.1%)
Enzalutamide	–	29 (9.2%)
Radium-223	–	4 (1.3%)
Total number of life-prolonging treatments, n (%)		
0	206 (99.5%)	235 (74.4%)
1	1 (0.5%)	38 (12.0%)
2	–	21 (6.6%)
3	–	14 (4.4%)
4	–	6 (1.9%)
5	–	2 (0.6%)

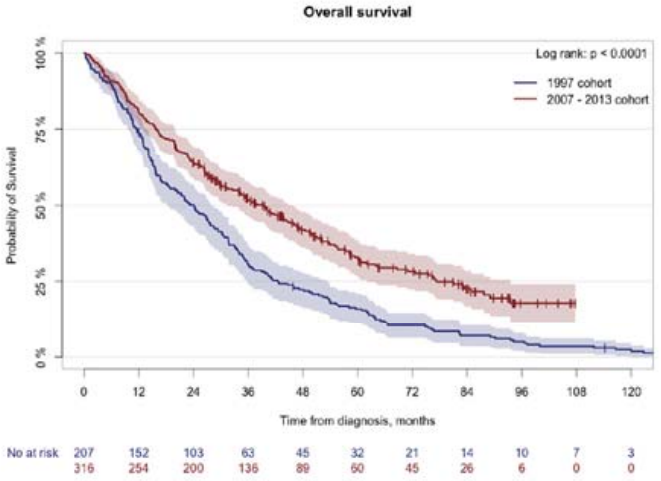

Fig. 1. Overall survival stratified by cohort.

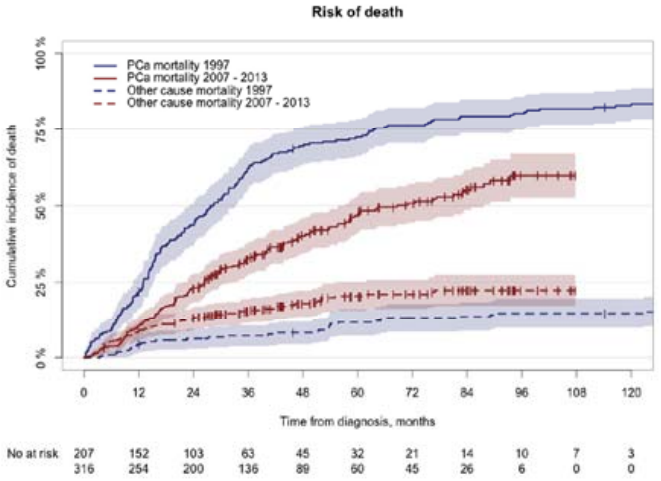

Fig. 2. Cumulative incidences of prostate cancer (PCa)-specific mortality (solid lines) and other-cause mortality (broken lines) stratified by cohort. Blue lines represent the historical cohort, whereas red lines represent the contemporary cohort.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

15.7–25.2) for men diagnosed in 1997 and between 2007 and 2013, respectively (Fig. 2).

In multivariable Cox regression analysis adjusting for age, PSA at diagnosis, CCI, cT category and primary treatment, men from the contemporary cohort had a 37% reduced hazard of death compared with men from the historical cohort (HR 0.63 [95% CI: 0.47–0.85], $p = 0.003$), Table 3. In a similar multivariable model, men diagnosed between 2007 and 2013 had a 43% reduced hazard of PCa-specific death compared with men diagnosed in 1997 (HR 0.57 [95% CI: 0.40–0.79], $p = 0.0009$), Table 4.

After excluding the 82 men who received life-prolonging therapies after progression on first-line treatment, subgroup analyses confirmed the improved survival among men in the contemporary cohort. Thus, 5-year cumulative incidences of PCa-specific mortality

Table 3
Overall survival Cox analyses including 183 men diagnosed in 1997 and 303 men diagnosed between 2007 and 2013 with complete baseline information.

Variable	Univariable analyses			Multivariable analysis		
	Hazard ratio	95% CI	*p* Value	Hazard ratio	95% CI	*p* Value
Diagnostic group						
1997	1	(ref)		1	(ref)	
2007–2013	0.59	(0.48–0.72)	<0.0001	0.64	(0.48–0.87)	0.004
Age; for 5 years diff.	1.10	(1.04–1.17)	0.002	1.07	(1.00–1.14)	0.04
PSA; for 2-fold diff.	1.12	(1.07–1.17)	<0.0001	1.11	(1.05–1.16)	<0.0001
Charlson co-morbidity index						
0	1	(ref)		1	(ref)	
1	1.27	(1.01–1.59)	0.042	1.20	(0.95–1.52)	0.13
≥2	1.59	(1.22–2.09)	0.001	1.45	(1.10–1.93)	0.009
Clinical tumour category						
cT1	1	(ref)		1	(ref)	
cT2	1.41	(1.02–1.96)	0.04	1.31	(0.94–1.83)	0.11
cT3	1.33	(0.95–1.87)	0.09	1.33	(0.94–1.89)	0.10
cT4	1.50	(1.02–2.20)	0.04	1.27	(0.85–1.90)	0.24
Primary treatment						
LHRH treatment	1	(ref)		1	(ref)	
Surgical castration	1.49	(1.19–1.87)	0.001	0.86	(0.62–1.18)	0.33
Total androgen blockade	1.33	(0.89–1.99)	0.16	1.11	(0.72–1.73)	0.64
Androgen receptor inhibitor	1.12	(0.65–1.94)	0.68	0.75	(0.41–1.39)	0.36
Oestrogens	1.70	(0.42–6.86)	0.46	1.21	(0.29–5.06)	0.79

Abbreviations: CI = confidence interval; PSA = prostate-specific antigen.

Table 4
Prostate cancer specific survival – cause specific Cox analyses including 183 men diagnosed in 1997 and 303 men diagnosed between 2007 and 2013 with complete baseline information.

Variable	Univariable analyses			Multivariable analysis		
	Hazard ratio	95% CI	*p* Value	Hazard ratio	95% CI	*p* Value
Diagnostic group						
1997	1	(ref)		1	(ref)	
2007–2013	0.50	(0.39–0.62)	<0.0001	0.57	(0.40–0.79)	0.0009
Age; for 5 years diff.	1.05	(0.98–1.12)	0.21	1.01	(0.94–1.09)	0.77
PSA; for 2-fold diff.	1.17	(1.12–1.23)	<0.0001	1.15	(1.10–1.22)	<0.0001
Charlson co-morbidity index						
0	1	(ref)		1	(ref)	
1	1.18	(0.92–1.52)	0.20	1.14	(0.88–1.48)	0.33
≥2	1.04	(0.74–1.47)	0.81	0.93	(0.65–1.32)	0.67
Clinical tumour category						
cT1	1	(ref)		1	(ref)	
cT2	1.25	(0.87–1.79)	0.23	1.14	(0.78–1.66)	0.50
cT3	1.26	(0.87–1.82)	0.23	1.26	(0.86–1.85)	0.24
cT4	1.47	(0.96–2.25)	0.08	1.24	(0.80–1.93)	0.34
First-line treatment						
LHRH treatment	1	(ref)		1	(ref)	
Surgical castration	1.72	(1.33–2.22)	<0.0001	0.96	(0.67–1.38)	0.84
Total androgen blockade	1.63	(1.06–2.51)	0.03	1.28	(0.80–2.06)	0.31
Androgen receptor inhibitor	1.31	(0.72–2.37)	0.38	0.72	(0.37–1.41)	0.34
Oestrogens	2.30	(0.57–9.32)	0.24	1.38	(0.33–5.84)	0.66

Abbreviations: CI = confidence interval; PSA = prostate-specific antigen.

were 72.7% (95% CI: 66.6–78.9) and 46.3% (95% CI: 39.3–53.2), respectively, $p < 0.0001$, and in the multivariable Cox regression analysis contemporary patients had a 40% reduced hazard of PCa-specific death (HR 0.60 [95% CI: 0.43–0.86], $p = 0.0009$).

The 5-year relative survival improved significantly over time, with an increase from 25% (95% CI: 18–34) for men diagnosed in 1997 to 45% (95% CI: 34–58) for men diagnosed between 2007 and 2013 (Fig. 3).

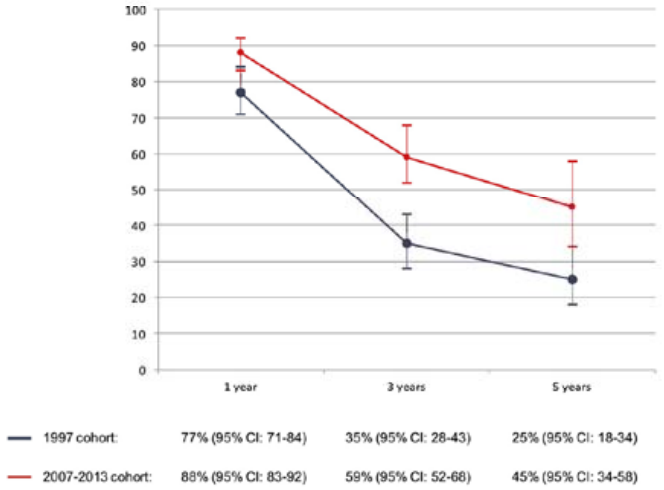

Fig. 3. The relative survival of metastatic prostate cancer patients diagnosed in 1997 (blue line) and 2007–2013 (red line) compared with an aged-matched standardised background population.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

The increased diagnostic activity has caused a significant reduction in the clinical tumour stage at the time of diagnosis. Still, recent Danish data have demonstrated that 13.7% of newly diagnosed PCa patients have bone metastasis at the time of diagnosis [17]. In the present study, we found that both overall survival and PCa-specific survival have improved over time for men presenting with *de novo* mPCa.

In the historical cohort, we found a median overall survival of 24 months, which is comparable with previous Danish results [18] but lower than reported in the SWOG8894 study, where the median survival was 30 months [19]. Patients in the historical cohort had higher PSA levels than the patients in the SWOG study (median 258 ng/ml versus 130 ng/ml), which indicates that the patients in the present study presented with a more advanced tumour burden. This may explain some of the differences in survival, as risk stratification based on PSA, performance status, and appendicular disease have a significant impact on survival [20]. In the contemporary cohort, we found a significant longer median survival (39 months) corresponding to an approximately 40% increase in overall survival when compared with the historical cohort. Still, this is somewhat shorter than the median survival, ranging from 42 to 54 months reported in the control arms of the STAMPEDE, CHAARTED and GETUG-AFU 15 studies [21–23] and the 67-month survival found in a recent Danish cohort study [24]. Again, the most apparent explanation is the inter-study differences in tumour characteristics clearly manifested in the median diagnostic PSA levels ranging from 26 to 112 ng/ml in the aforementioned studies [21–24] compared with 158 ng/ml in the present study. The higher PSA levels in both cohorts of the present study compared with other studies likely reflect differences in diagnostic strategies. This is supported by recent findings demonstrating that Danish patients generally have higher PSA levels and lower survival rates than Swedish and Icelandic men diagnosed during the same period [12].

Our study has some limitations, including those inherent to its retrospective and observational nature. First, differences in PCa awareness, referral patterns and available treatment options over time may result in inter-cohort tumour differences and confounders that are not fully accounted for in the statistics. Second, as data were derived for registers and patients' charts, we were not able to include important variables, such as performance status, symptoms and the presence of visceral metastases into our analyses. Finally, because of the retrospective study design, it was impossible to adjust for any differences in histological grading between the two cohorts. Men diagnosed in 1997 were predominantly graded according to the WHO classification, whereas men diagnosed in the period 2007–2013 were graded according to the Gleason grading system. Previous studies have unsuccessfully attempted to translate WHO grades into Gleason scores [12]; thus, reclassification was not performed. Furthermore, men diagnosed in 1997 had a significantly higher median PSA level at diagnosis indicating differences in tumour burden and metastatic load, which might affect their prognosis [25,26].

During the study period, the awareness of PCa in Denmark has risen in general [27], curative treatment has been fully implemented, and early diagnosis through clinical staging has been more predominant. This approach has led to a more intensive use of imagining in the work-up for curative treatment: between the two study periods, a shift towards a more aggressive treatment of PCa has occurred—only 2% of men diagnosed in 1997 received curative treatment, increasing to 33% of patients diagnosed in 2007–2013 [12,27]. Furthermore, although Danish authorities have recommended against PSA screening during both study periods, previous studies clearly indicate that opportunistic PSA testing is ongoing and has increased over time [12,13,28]. Consequently, the diagnosis of the contemporary cohort may be influenced by some degree of unauthorised PSA testing, which is reflected in the lower tumour burden and lower PSA level compared with the historical cohort. Thus, the survival advantage demonstrated in the contemporary cohort is most likely the result of a combination of lead-time bias and effective therapy. A further support of the impact of lead-time bias is the sustained difference in prognosis between the two included cohorts after excluding the 82 patients who underwent life-prolonging therapies.

We found a significant difference in the choice of ADT between the two cohorts. This difference is, however, unlikely to have had any major impact on the survival, as a meta-analysis including 1539 men from 12 randomised controlled studies comparing GnRH agonists with orchiectomy found no difference in overall survival between the two treatments, HR 1.26 (95% CI: 0.92–1.39) [29]. In contrast, the 8% of the men diagnosed in 1997 who were primarily treated with androgen receptor inhibitors or oestrogens might have had an impaired prognosis due to the choice of primary treatment [30].

Following positive phase III studies, new treatment options have been gradually introduced in men with metastatic CRPC. However, previous reports have demonstrated a lower efficacy when the agents are used outside a clinical trial setting, which is likely explained by differences in patient selection [31,32]. Although the new treatment options have been available in Denmark for the time period of the contemporary cohort, only one in four men with mPCa received second-line therapy. The median time from initiating ADT to the development of CRPC has been reported to be approximately 1–2 years [21,22,33]. Thus, it is possible that some patients from the contemporary cohort are still hormone sensitive and thus may be considered eligible candidates for second-line therapies in the future, as the patients have been observed for at least 2 years and approximately 20% are not deceased. The overall low use of second-line therapies is unlikely to be caused by comorbidity, as most of the patients had limited comorbidity at diagnosis. More likely, patient preferences and perhaps certain reluctance against chemotherapy both among patients and physicians can explain the low percentage of patients having chemotherapy. Moreover, the percentage of patients managed with second-line therapies is comparable with recent Swedish figures demonstrating that approximately 20% of patients eventually dying from PCa have been treated with docetaxel [34].

Our results demonstrate that the prognosis for contemporary men diagnosed with mPCa has improved compared with historical patients both in terms of overall survival and PCa-specific survival. In contrast, other-cause mortality has remained almost unchanged during the study period. The main contributor to the observed 15-month difference in median survival between the two cohorts is most likely not the implementation of the new life-prolonging agents: only 25.6% of the contemporary cohort has received second-line therapies, and the survival gains reported in the phase III trials are in the range of 1.9–4.2 months [4,5,7,8]. Thus, lead-time bias and differences in metastatic burden are likely to have had the largest impact on the survival difference observed. Moreover, socioeconomic selection bias between the cohorts cannot be excluded, as the historical cohort is nationwide, whereas the contemporary cohort originates from an urban area. Nonetheless, the new treatments seem to positively influence survival, as the contemporary cohort had a lower hazard of PCa-specific mortality compared with the historical cohort, even after adjusting for differences in diagnostics characteristics. This underlines the positive impact of second-line therapies on survival, when used outside a clinical study as well, and it can be anticipated that the survival can be further improved as the new agents become more widely implemented.

Furthermore, upfront combined chemo-hormonal therapy has been demonstrated to improve survival in patients with mPCa significantly [22,23,35], and with the increasing number of treatment options available when primary therapy fails, the need for studies on optimising sequencing becomes obvious.

5. Conclusion

Survival in men diagnosed with mPCa has improved significantly over time. The improved survival can primarily be explained by the lower tumour burden at diagnosis, but also by the introduction of new life-prolonging treatments.

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Conflicts of interest statement

None declared.

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Appendix I

APPENDIX 1

Figure 1

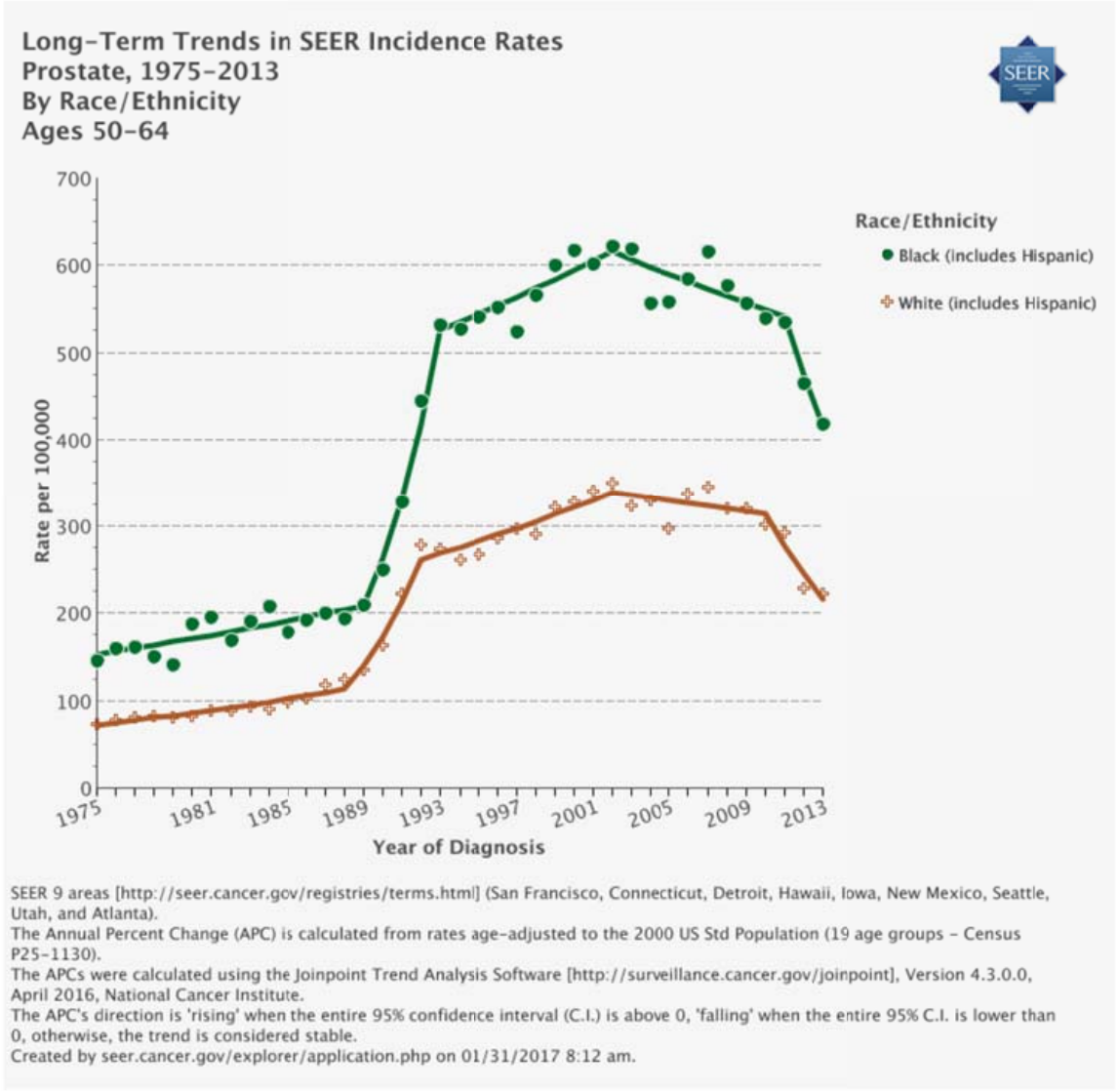


Figure 2

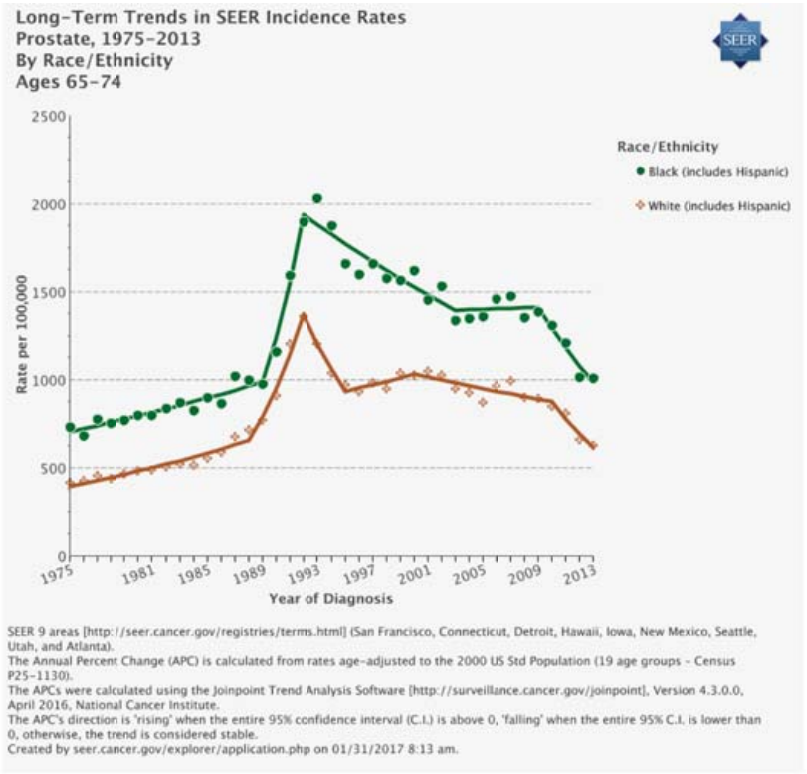
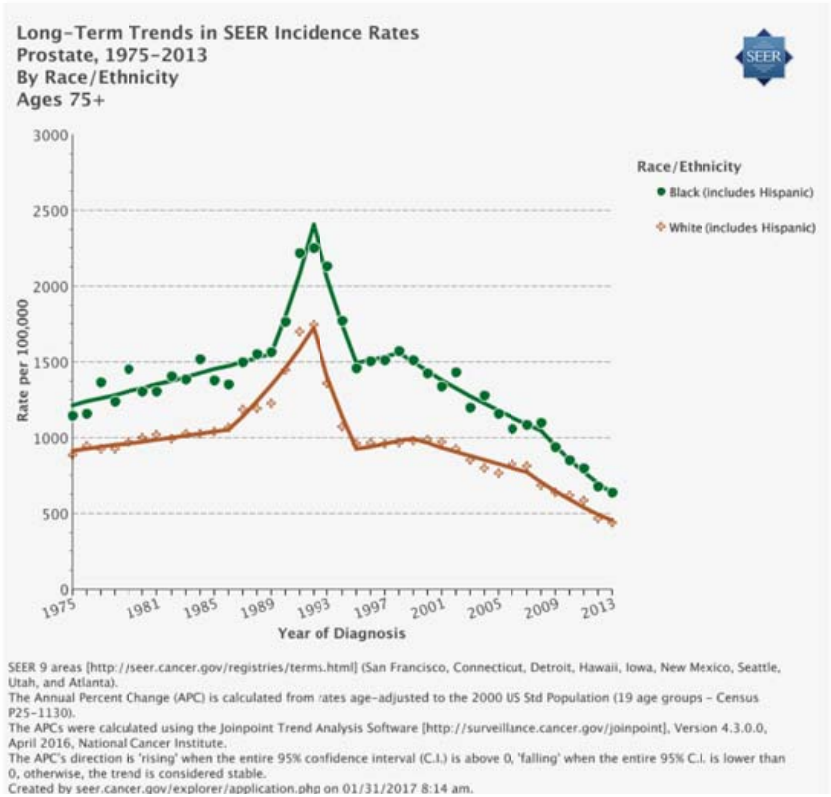


Figure 3



Stage Distribution of SEER Incidence Cases
Prostate, 2004-2013
Race/Ethnicity
All Ages

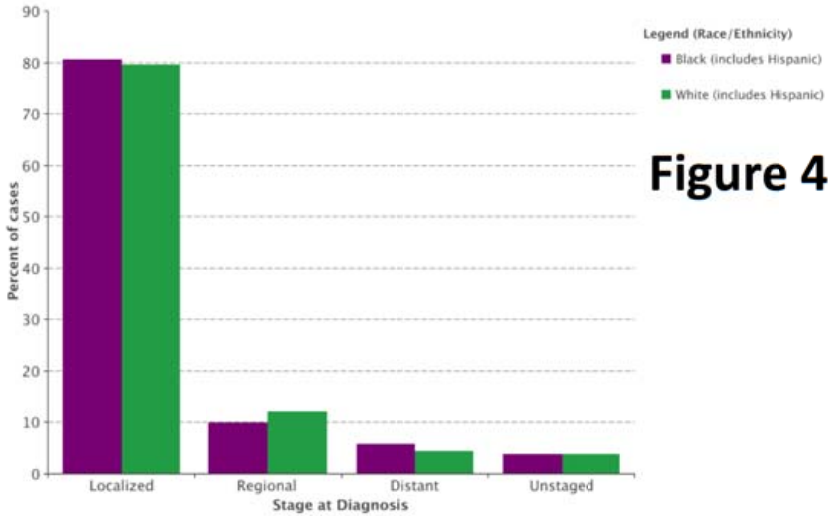


Figure 4

SEER 18 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
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Stage Distribution of SEER Incidence Cases
Prostate, 2004-2013
Race/Ethnicity
Ages 50-64

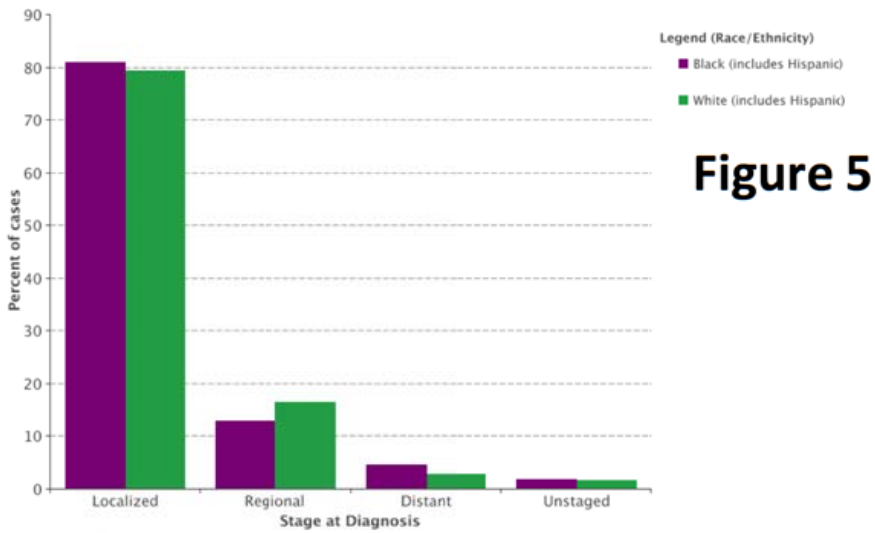

Figure 5

SEER 18 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
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APPENDIX 1

Stage Distribution of SEER Incidence Cases
Prostate, 2004-2013
Race/Ethnicity
Ages 65-74

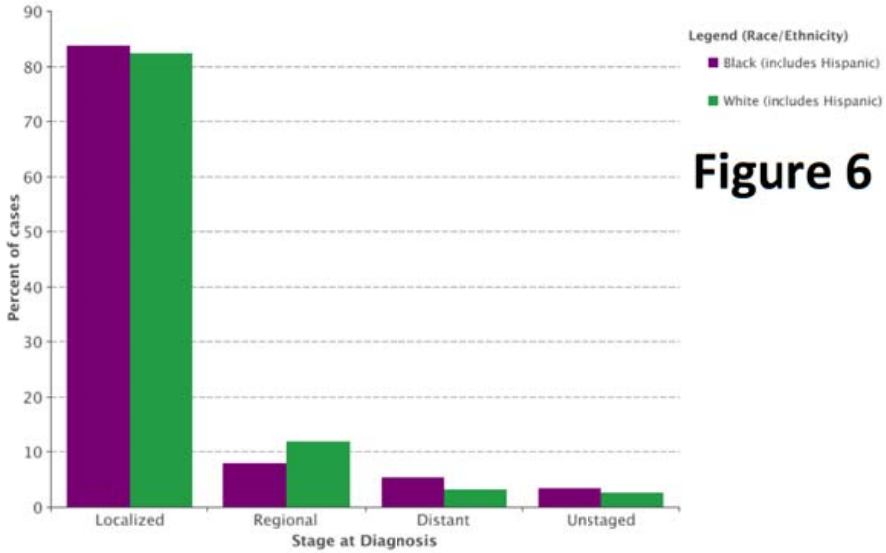

Figure 6

SEER 18 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
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Stage Distribution of SEER Incidence Cases
Prostate, 2004-2013
Race/Ethnicity
Ages 75+

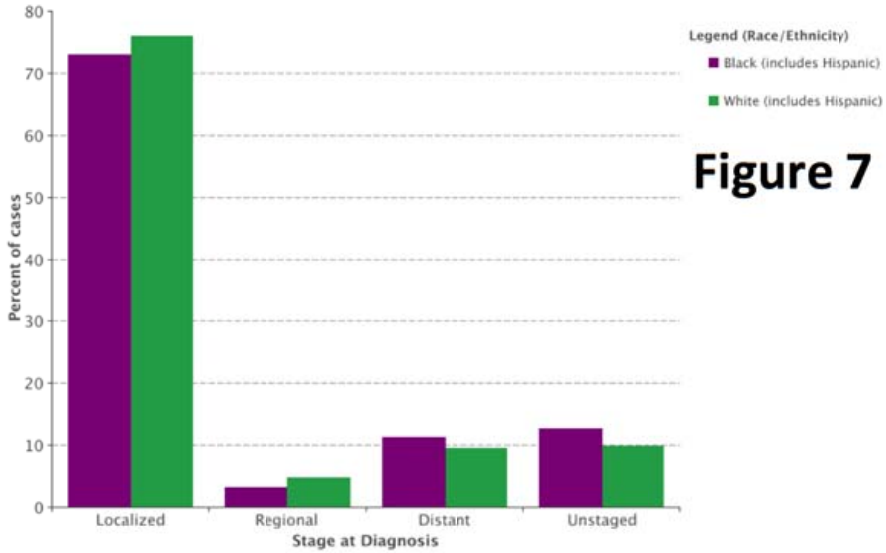

Figure 7

SEER 18 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
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APPENDIX 1

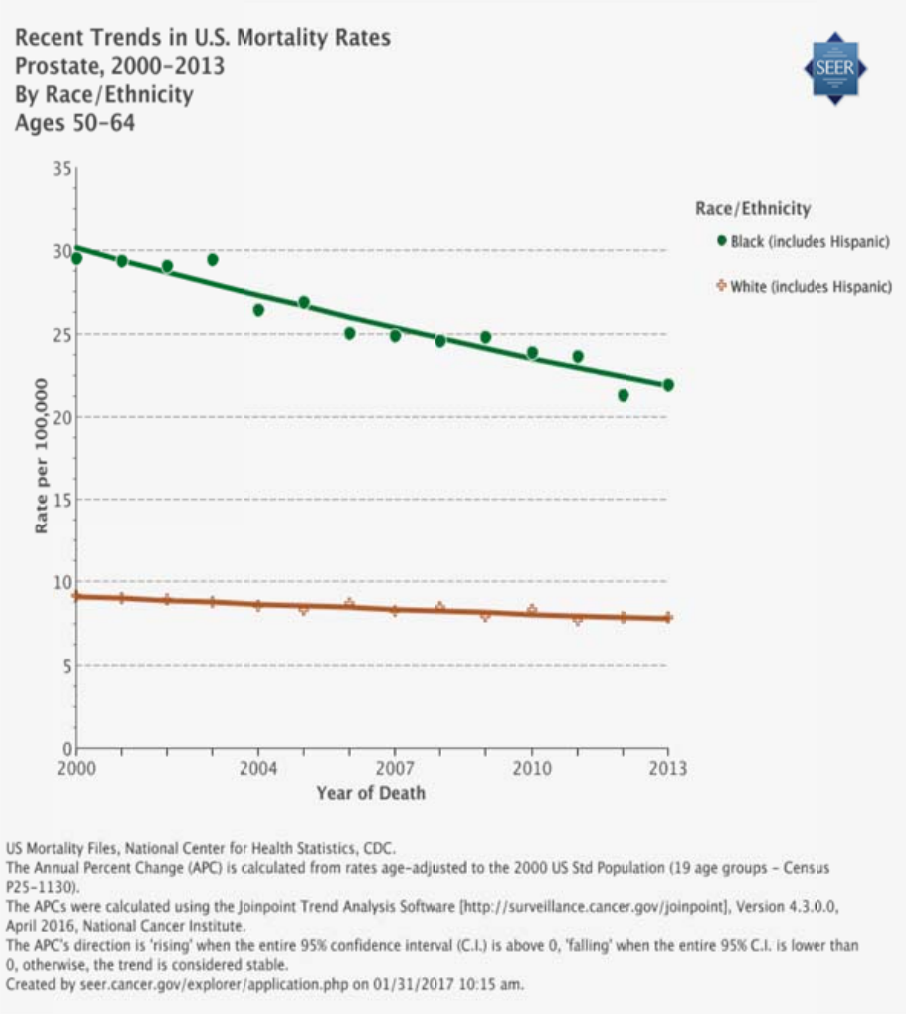


Figure 8

Figure 9

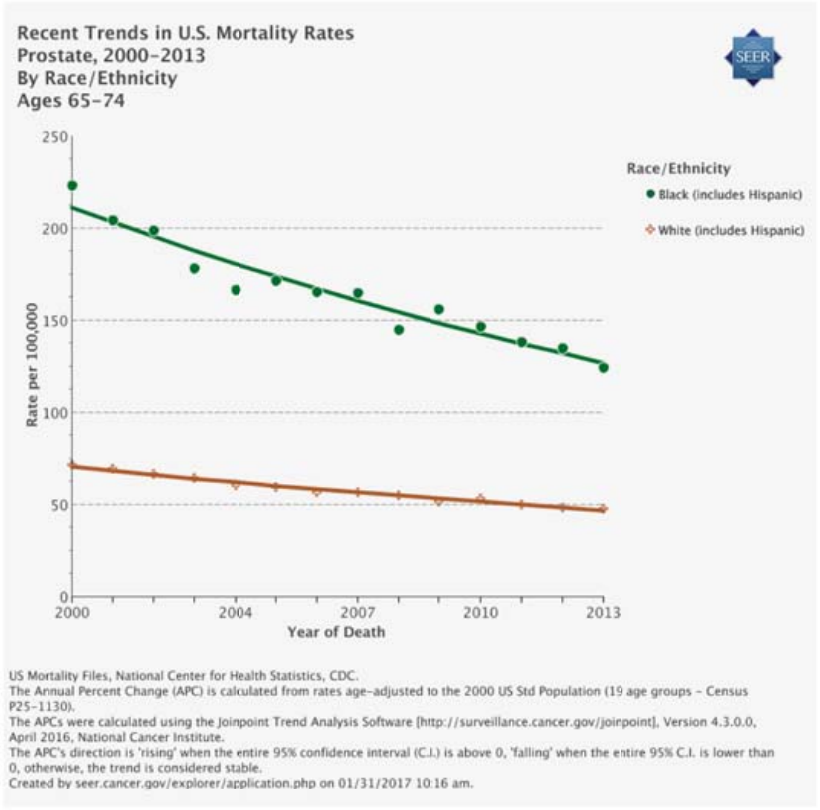
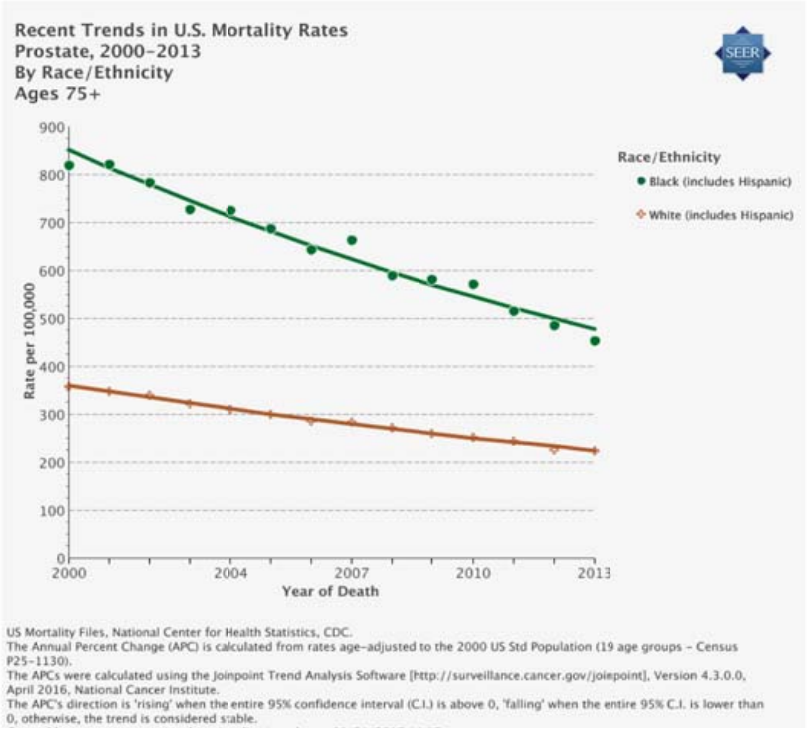


Figure 10



Appendix II

PROSTATE CANCER STUDY

COUNTRY ☐☐

STUDY NUMBER ☐☐ SERIAL NUMBER ☐☐☐☐

ABSTRACTOR ☐☐

BIRTH DATE ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

DATE FOR FINISHING ABSTRACTION

☐☐ DAY ☐☐ MONTH ☐☐ YEAR

HOSPITAL/CLINIC I.D. ☐☐☐☐☐

COMMENTS OUTSIDE THE BOXES IN THIS QUESTIONAIRE ☐ YES

---

1. PATIENT DATA

1a. FAMILY HISTORY OF PROSTATE CANCER
(more than one box can be ticked)

☐ NONE ☐ 1. GRADE REL. ☐ 2. GRADE REL. ☐ BOTH ☐ UNKNOWN

1b. HEIGHT AND WEIGHT

☐☐☐ CM ☐☐☐ KG

1c. COMPETITIVE DISEASE(S) AND TYPE(S):
(more than one box can be ticked)

☐ NONE ☐ LUNG ☐ HEART ☐ ARTERIAL ☐ DIAB. ☐ COLL. ☐ PSYCH ☐ OTHER

IF OTHER, SPECIFY:_____

☐ UNKNOWN

---

2. FIRST CONTACT

2a. MODE OF DETECTION OF TUMOR
(Only tick one box below)

PATIENT'S SYMPTOMS (e.g. strangury, dysury, pollakisury, pain) ☐

CONSEQUENCE OF INCIDENTAL PSA TESTING ☐ PSA-VALUE ng/dl ☐☐☐☐

DETECTED BY DOCTOR AT VISIT FOR OTHER REASON (Includes patients diagnosed because of symptoms discovered while in hospital for another reason) ☐

CONSEQUENCE OF BPH FOLLOW-UP (Including incidental TURP findings) ☐

OTHER: _____ ☐
specify

---

3. BIOPSY

3a. FIRST BIOPSY (Only one tick) ☐ primary tumour ☐ metastasis ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

TYPE ☐ NONE ☐ FNA ☐ BMA ☐ TRU-CUT ☐ TURP ☐ NOT SPECIFIED

3b. HISTOLOGY (ICDO-CODE) ICDO CODE ☐☐☐☐☐

SNOMED CODE: (AC) 81403, (SCC) 80703, (LP) 81423, (ICAC) 814443, (DA) 81453, (TC) 82113, (C.OID) 82403, (GCC.OID) 82433, (PAP.AC) 82603, (MU.EP:C) 84303, (MUC.AC) 84803, (SIGIL.C.AC) 84903, (ASCC) 85603, (MM) 87203, (LMS) 88903, (ML) 95903

3c. GRADING

GLEASON SCORE ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

OR

GRADE ☐ WELL DIFF. ☐ MODERATE ☐ POOR DIFF. ☐ UNKNOWN

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4. CLINICAL AND DIAGNOSTIC EXAMINATIONS

4a. TNM STATUS T☐ N☐ M☐ ☐ INDIC. ☐ RECONSTRUCTED

4b. METASTATIC SITES: (more than one OK) ☐ Bone ☐ Lung ☐ Liver ☐ Skin ☐ Brain ☐ Other _____ specify

DIAGN. EXAMINATIONS	Done	Not done	Unknown
4c. TRANS-RECTAL ECHOGRAPHY (or other prostate imaging)	☐	☐	☐
4d. ABDOMINAL CAT-SCAN (or other imaging for abdominal nodes)	☐	☐	☐
4e. BONE SCINTIGRAPHY	☐	☐	☐
4f. MULTIPLE BONE X-RAY	☐	☐	☐
4g. LYMPHADENECTOMY	☐	☐	☐

Total number of lymph nodes examined ☐☐ Number of metastatic lymph nodes ☐☐

OR Any metastatic lymph nodes ☐ YES ☐ NO

4h. PSA BEFORE THERAPY (prostate-specific-antigen)	☐	☐	☐

PSA-value ng/dl ☐☐☐☐

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5. PRIMARY TREATMENT

5a. INCLUDED IN A CLINICAL TRIAL ☐ YES ☐ NO ☐ NOT SPECIFIED

5b. DOCUMENTED DISCUSSION WITH PATIENT ABOUT TREATMENT AND POTENTIAL SIDE EFFECTS ☐ YES ☐ NO ☐ UNKNOWN

5c. PLANNED RADICAL TREATMENT ☐ YES ☐ NO ☐ UNKNOWN

5d. SURGERY (TYPE and DATE) ☐ RADICAL PROSTATECTOMY ☐ OTHER _____ specify ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

5d.1 PATHOLOGICAL TNM ☐ T2a ☐ T2b ☐ T3a ☐ T3b ☐ T4 ☐ Tx

5d.2 POSITIVE RESECTION BORDERS ☐ YES ☐ NO

5d.3 GRADING

GLEASON SCORE ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

OR

GRADE ☐ WELL DIFF. ☐ MODERATE ☐ POOR DIFF. ☐ UNKNOWN

5d.4 NO SURGERY HAS BEEN PERFORMED BECAUSE OF:

☐ Patient´s refusal to be treated or death ☐ Explicitly mentioned medical contraindications ☐ Metastasis ☐ Other or unspecified reasons (e.g. it may be the best option)

5e CURATIVE RADIOTHERAPY

TYPE and DATE ☐ BRACHYTHERAPY ☐ EXTERNAL RT ☐ UNKNOWN ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

5e.1 TOTAL RADIOTHERAPY DOSIS ☐☐☐☐ Gy

5e.2 NO CURATIVE RADIOTHERAPY HAS BEEN PERFORMED BECAUSE OF:

☐ Patient´s refusal to be treated or death ☐ Explicitly mentioned medical contraindications ☐ Metastasis ☐ Other or unspecified reasons (e.g. it may be the best option)

5f. NEO-ADJUVANT ENDOCRINE TREATMENT

☐ YES ☐ NO

START DATE ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

END DATE ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

6. OTHER THERAPY

6a. HORMONAL THERAPY
(START/OPERATION DATE) ☐ NO ☐ YES ☐ UNKNOWN, ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

6a.1 TYPE

1 BILATERAL ORCHIECTOMY ☐

2 LHRH TREATMENT ☐

3 ANTI ANDROGENE MONO THERAPY ☐

4 MAXIMAL ANDROGENE BLOCKING ((1 or 2) plus 3) ☐

5 PARENTERAL ESTROGENE ☐

6 ANTI FLARE TREATMENT (2 and 3 in 4 weeks) ☐

7 OTHER SPECIFIED TREATMENT ☐ IF YES TYPE _____

6a.2 NO HORMONAL THERAPY HAS BEEN PERFORMED BECAUSE OF:

☐ Patient´s refusal to be treated or death ☐ Explicitly mentioned medical contraindications ☐ Other or unspecified reasons (e.g. it may be the best option)

6b. CHEMOTHERAPY
(START DATE) ☐ NO ☐ YES ☐ UNKNOWN ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

IF YES, INDICATE TYPE ☐ TAX ☐ CMF ☐ CEF ☐ OTHER _____ specify

6b.1 NO CHEMOTHERAPY HAS BEEN PERFORMED BECAUSE OF:

☐ Patient´s refusal to be treated or death ☐ Explicitly mentioned medical contraindications ☐ Other or unspecified reasons (e.g. it may be the best option)

6c. TURP
(DATE) ☐ NO ☐ YES ☐ UNKNOWN ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

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7. RECURRENT PROSTATE CANCER

7a. LOCAL/REGIONAL RECURRENCE ☐ NO ☐ YES ☐ UNKNOWN

DATE OF VERIFICATION ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

7b. DISTANT METASTASES ☐ NO ☐ YES _____ if yes site ☐ UNKNOWN

DATE OF VERIFICATION ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

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8. LAST CONTACT IN HOSPITAL PAPERS

☐☐ DAY ☐☐ MONTH ☐☐ YEAR

Appendix III

Guidelines for collecting clinical data for the NORDCARE project on prostate cancer in Denmark

January 25th 2005
Written by stud.med. Inga Jóna Ingimarsdóttir

General instructions for study forms to be scanned

Completed study forms will be scanned so please be careful when you fill in the answers.
In big boxes one number or letter should be filled in. Beware that the number or letter does not coincide with the walls of the box and write distinct to avoid mistakes to take place in the interpretation by the scanner program.
In small boxes only x should be used.
If you feel that you have to explain something about the answers, you can do it outside the boxes. It will be scanned and kept as a picture, but with no interpretation by the scanner program. The message will only be read later if some inconsistencies in the data for that person make us look for further information.

PROSTATE CANCER STUDY
Abstractor: II (Inga Jóna Ingimarsdóttir) or TG (Tora Grauers)

Birth date: We operate with two main types of lists; one with the study number of the patient and information on which hospital department reported the cancer diagnosis to the Danish Cancer Registry, and one with the study number and full name and CPR number of individual patients. Using the study number as identifier, the patients CPR number and thus birth date can be retrieved.

Hospital/Clinic I.D.: Using the study number as identifier, information can be obtained on which hospitals/hospital departments have reported the prostate cancer diagnosis to the Danish Cancer Registry. All hospital departments are noted on the form. Medical records on each patient are ordered from all departments involved and reviewed thoroughly.

Comments outside the boxes in this questionnaire: Occasionally it can be helpful to write commentaries outside the boxes, as they can facilitate establishment of a full picture of the clinical course, especially when the patient has been treated in several different hospital departments. After scanning of the completed data form, pictures of the scanned pages will be available electronically. A mark in the box will indicate that extra information is available.

1. PATIENT DATA

1a. Family history of PC: In the medical record, examine under predispositions if there is any information on prostate cancer in the patients family. If no information is provided for predispositions, mark the box "unknown". If there is information about diseases other than prostate cancer, mark the box "none".

1b. Height and weight: This information is often noted in the nurses' files. Sometimes it can also be found in the oncology records, but then it is of great importance to note the period from prostate cancer diagnosis until admission/referral to the oncology department. In the meantime, the patient may have suffered a considerable weight loss, and therefore the value cannot be used. The height is more reliable.

1c. Competitive disease(s) and type(s): In the medical record look under "earlier hospitalization/diseases". Information on other diseases can often be found in the text. Note that COLL stands for collagen disease.

2. FIRST CONTACT

2a. Mode of detection of tumour: It can be difficult to ascertain what first led to the diagnosis of prostate cancer. In Denmark, the first signs are often lower urinary tract symptoms (LUTS), for which the patient consults his general practitioner, who subsequently refers the patient to an urologist. First suspicion by PSA testing is not frequent.

3. BIOPSY

3a. First biopsy: This is the histology report that establishes the prostate cancer diagnosis. Under "date of diagnosis" write the date on which the tissue biopsy was performed, but not the date where the pathology report was issued. If the biopsy is from the prostate (the primary tumour) mark the box "TRU-CUT". Fine needle aspirate (FNA) is often extracted from non-regional lymph nodes, and if the specimen shows prostate cancer cells, mark the box "metastasis". Mark the box "BMA" when cancer cells are detected in the bone marrow, and mark "TURP" if there are malignant cells in the resected prostate chips. If the diagnosis is based on clinical examination alone, mark the box "none". Only one box can be marked. The date registered should then be the date that the patient was referred to or admitted to hospital for suspicion of prostate cancer.

3b. Histology: Should not to be filled in at this time. This information can be obtained later from the pathologists. The ICD-O code is not registered in the pathology reports based on prostate cancer specimens.

3c. Grading: Information on grading should always be available in the pathology report. Sometimes the pathologist issues a first report without grading, however, the information should then be available in a more detailed pathological report issued later. Grading is presented as Gleason scores. The higher the Gleason score, the lower the differentiation of the tissue. Alternatively grading may be recorded using the WHO-system, and the terms stated in the pathology report shall be used. If the pathology report reads "moderate to low differentiation", mark the box "low" as it is more aggressive than "moderate". Only use the box "unknown" when no information about grading is found, or if the pathology report is not available. Occasionally paper copies of medical records received from other hospitals arrive without the pathology report. Usually, however, information on grading can also be found elsewhere in the medical record, especially in the doctors´ correspondence. However, it may be necessary to require the information from the original pathology department. It is

done by referring to the patients CPR number, the original hospital department he was admitted to, and the period in which the histology specimen was taken.

4. CLINICAL AND DIAGNOSTIC EXAMINATIONS

4a. TNM status:
A TNM classification noted by the physician who made the diagnosis should be registered (and the box "indic." marked), unless there is contradictory information in the medical records. If the abstractor disagrees with the TNM classification, a specialist (urologist or oncologist) at the particular hospital or doctors at the Danish Cancer Society should be consulted.

Clinical T-stage is determined by a combination af digital rectal examination (DRE) and ultrasonography. If different stages are stated, the T-stage as determinated by a senior urologist should be accepted.
Stages reflect the size of the tumor

T1, nonpalpable tumors,

T1a < 5% of resected chips following TURP
T1b > 5% of resected chips following TURP
T1c, positive biopsy findings following elevated PSA

T2, palpable, organconfined tumors,

T2a, only one lobe positive
T2b, both lobes positive

T3, palpable, tumors extending beyond the boundaries of the prostate

T3a, extracapsular extension
T3b, invasion in the seminal vesicles

T4, palpable tumor invading in or fixed to pelvic organs

N-stage reflects tumour involvement in the lymph nodes

NX: No assessment of lymph node status has been performed
N0: No positive lymph nodes
N1: Cancer in lymph nodes

N1 status is only to be recorded if a positive lymph node can be demonstrated, or if an abdominal CT-scan states that the lymph nodes are grossly involved

M-stage reflects distant metastasis

MX: No assessment has been performed
MO: No signs of metastasis on bone-scan
M1: Any positive finding of distant metastasis either bone scan or CT-scan demonstrating viseral metastasis.

If no stage is stated in the records, the abstractor determines the stage

4b. Metastatic sites: Mark the boxes representing the organs where distant metastasis has been detected.

DIAGN.EXAMINATIONS

4c. Trans-rectal echography: Includes rectal ultrasound or other imaging of the prostate. Prostate biopsy are usually performed per rectum guided by ultrasound

4d. Abdominal CAT-SCAN: CT or other imaging of the abdominal lymph nodes. CT can confirm, but not exclude lymph node metastases.

4e. Bone scintigraphy: Bone scintigraphy, performed to demonstrate or exclude bone metastases.

4f. Multiple bone x-ray: Multiple x-rays of the skeleton, in which metastases can be observed as sclerotic or osteolytic changes.

4g. Lymphadenectomy: Removal and histological examination of regional lymph nodes to determine whether there are involvement of lymph nodes. The pathology report sometimes states number of lymph nodes examined and how many were malignant. Fill in the relevant boxes. Sometimes it is only stated whether the lymph nodes were benign or malignant; then fill in "yes" or "no".

4h. PSA before therapy:

Fill in the PSA value closest to the date of diagnosis. Usually, it can be found in the blood test sheet under "diverse". It is helpful to add the date of the test result outside the boxes in case a test value closer to the date of diagnosis is subsequently identified.

5. PRIMARY TREATMENT

5a. Included in a clinical trial: It should be clearly apparent from the text of the medical record and also doctors' correspondence if the patient was enrolled in a clinical trial.

5b. Documented discussion with a patient about treatment and potential side effects:

Information on which treatments are possible in relation to the severity of the disease, and advantages and adverse effects of the various therapeutic possibilities. There is no difference between the answers "no" and "unknown", because if the doctor has informed about all the aspects of a given treatment, he has to document this in the case record. "Yes" can only be filled in if the information is stated in the medical record.

5c. Planned radical treatment:

The patient has been offered curative intended radical removal of prostate by surgery or curative radiotherapy of the prostate (These radical treatment offers will be carried out only if no sign of spreading of the cancer is found).

Section 5d.1-5d.4 should only be filled in if radical prostatectomy was planned.

5d. Surgery (type and date):

Mark "radical prostatectomy" if the patient has undergone this procedure. If the patient only had lymphadenectomy, mark "other" and in the "specify" field write

"lymphadenectomy". Fill date of radical prostatectomy or other surgery (typically perioperative lymphadenectomy).

5d.1 Pathological TNM:
Same classification criterion as in clinical T stage. It should be found in the pathology result. See comment above (4a)

5d.2 Positive resection borders: The pathology report states if the cancer has grown through the resection border.

5d. 3 Grading:
Stated under pathology results as Gleason score and/or WHO degree of differentiation.

5d. 4 No surgery has been performed because of:
Mark box no. 1 if the patient denied an offer for operation or died. Mark box no. 2 if the patient had concurrent morbidity which hindered operation. Mark box no. 3 if positive lymph nodes were found during the lymphadenectomy, and consequently surgery was cancelled. Finally, mark box no. 4 if the first two options are not indicated, i.e. the medical records do not indicate why the operation was not performed.

5e Curative radiotherapy
If curative radiotherapy has been given, the medical record from the oncology department should state type of radiation, treatment period and total radiation dose.

Section 5e.1- 5e.2 should only be filled in if curative radiotherapy was planned.

5e.1 Total radiotherapy dose:
In Gy (Gray); it should be reported in the oncology record.

5e.2 No curative radiotherapy has been performed because of:
Same options as for radical prostatectomy, section 5d.4.

5f. Neo-adjuvant endocrine treatment:
Anti-androgen medication is often given prior to curative intended radical prostatectomy or curative radiotherapy to shrink the prostatic gland.

6. OTHER THERAPY

6a. Hormonal therapy (start/operation date):
Primary hormonal therapy. The date (or month) treatment was offered and whether the patient accepts or denies; is usually clearly stated in the medical record.

6a.1 Type
1. Bilateral orchiectomy:
Surgical castration; it should be clearly stated in the medical record under "operations".

2. LHRH treatment:
Relevant drugs in Denmark are Zoladex, Decapeptyl, Enantol, Procren and Soprefact. Most frequently Zoladex is used as a three months depot injection. Typically, anti-androgen therapy is given during the first four weeks followed by LHRH-injections. These compounds can be given for a longer time period.

3. Anti-androgen treatment:
Relevant drugs in Denmark are Casodex, Nilutamid, Flutamid, Eulexin, Fluprosin, Androcur and Profamid. Casodex is most frequently used.

4. Maximal androgen blocking (1/2 + 3):
This is a very frequent and effective combination of hormonal therapy. Most often Casodex is given for four weeks, then supplemented by Zoladex. Some patients may undergo orchiectomy and continue with Zoladex injections.

5. Parenteral oestrogen:
Metastatic prostate cancer is the main indication. Preferred drug in Denmark is Estradiol (Estradurin, Østradiol (DAK)).

6. Anti flare treatment (2 and 3 for 4 weeks):
LHRH and anti-androgen for four weeks only.

7. Other specified treatment:
Other hormonal therapy.

6a.2 No hormonal therapy has been performed because of:
Not to be filled in.

6b. Chemotherapy (start date):
The oncology medical record states if the patient has received chemotherapy, but patients rarely receive this treatment. Normally patients receive hormonal therapy and palliative radiotherapy for metastatic prostate cancer. Possible regimens:
TAX: Taxotere (Docetaxel)
CMF: Cyclophosphamid + Methotrexate + Fluorouracil.
CEF: Cyclophosphamid + Farmorubicin (Epirubicin) + Fluorouracil.

6b. 1 No chemotherapy has been performed because of:
Not to be filled in.

6c. TURP (date):
The patient has undergone TURP after the prostate cancer diagnosis. In case the patient was originally diagnosed on basis of examination of prostate chips from primary TURP, this does not apply here.

7. RECURRENT PROSTATE CANCER
Not to be filled in.

8. Last contact in the case record (date):
To be used as the last follow-up date in analysis.