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FAMILY HISTORY AND PROGNOSIS OF PROSTATE CANCER

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Stockholm 2020

Family history and prognosis of prostate cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostatacancer är den vanligaste cancerformen bland män i Sverige. Av de cirka 10 000 män som diagnosticeras årligen avlider cirka 20–25% till slut av sjukdomen. För många män innebär att bli diagnosticerad med prostatacancer dock en god chans till att leva länge med sjukdomen. För närvarande beräknas drygt 100 000 män leva med prostatacancer i Sverige idag[1].

Prostatacancer har gått från att vara en obotlig sjukdom där endast symtomlindring är möjlig, till att kunna botas med operation eller strålbehandling. Stora framsteg har även gjorts i behandling av långt framskriden sjukdom där möjlighet till bot inte längre finns.

Det har länge varit känt att ha nära släktingar med prostatacancer ökar risken för att själv drabbas. I Cancerregistret som etablerades redan på 1950-talet kunde man efterhand se att prostatacancer är vanligt i vissa familjer. Ju fler nära släktingar med sjukdom, desto större risk att själv drabbas. Däremot har det varit svårt att studera om ärftligheten innebär en ökad risk för allvarlig prostatacancer. Eftersom prostatacancer ofta utvecklas långsamt och drabbar sent i livet, tar det lång tid innan det går att studera sjukdomen progress hos de, vars fäder avled i prostatacancer kanske 30 till 40 år tidigare. Diagnostik och behandling har också utvecklats över tiden vilket påverkar sjukdomsförloppet.

I slutet av 1990-talet började Nationella Prostataregistret (NPCR) ta form och fr.o.m. 1998 är alla regioner i Sverige inkluderade. Registret är idag ett nationellt kvalitetsregister med mer än 160 000 registrerade fall av prostatacancer. Med hjälp det svenska personnumret kan registret länkas samma med andra nationell register vilket möjliggör att studera prostatacancer utifrån olika folkhälsoaspekter och koppling till andra sjukdomar.

I denna avhandling presenteras 4 delarbeten med fokus på familjehistoria och prognos i prostatacancer. Med hjälp av en stor sammanlänkning av flertalet nationella register, PCBaSe, kan familjer med flera drabbade individer identifieras och jämföras avseende sjukdomsspecifika egenskaper.

I **delarbete 1** jämför vi den histopatologiska diagnosen mellan brödrapar där både har prostatacancer. Alla män som diagnosticerats med prostatacancer och som återfanns i NPCR 1996–2006 inkluderades. Bland dessa återfanns 1 022 brödrapar där båda hade prostatacancer. Vi fann att den relativa risken att drabbas av prostatacancer i någon form var cirka 3 gånger så stor för män med en bror med prostatacancer. För män med en bror med aggressiv prostatacancer var risken att själva drabbas av liknade sjukdom ca 4–5 gånger så hög.

I **delarbete 2** analyseras i vilken grad prostatacancer samvarierar mellan olika typer av bröder. (helbröder, halvbröder och tvillingar). Fallen diagnosticerades mellan 1996–2012. Vi fann 4 262 brödrapar, varav 58 par av enäggstvillingar och 38 par av tvåäggstvillingar. Vi delade in varje fall av prostatacancer i grupperna låg risk och icke låg risk. Gruppen icke låg risk består

av män med mellan- eller högrisk prostatacancer och som alltid bör erbjudas behandling. Analysen av brödraparen visade att för fullbröder var risken att ha en icke låg risk, behandlingskrävande prostatacancer var cirka 1,2 gånger högre. För enäggs- och tvåäggstvillingar var motsvarande siffra 3,8 och 1,4 gånger högre risk, dock inom den statistiska felmarginalen. Resultatet ska tolkas som den extra risk det innebär att diagnosticeras med icke lågrisk prostatacancer utöver den grundrisk på cirka 3 gånger högre risk att diagnosticeras med någon form av prostatacancer som vi fann i delarbete 1. Resultaten visade att det finns en trend i att ju mer arvsmassa som delas mellan bröderna, desto större samvariation i prostatacancer.

I **delarbete 3** ställde vi oss frågan om män med lågrisk prostatacancer löper högre risk att härbärgera en mer aggressiv tumör om de har förstagradssläktingar med prostatacancer. Tidigare studier har visat att cirka 30–40% av män som opereras visar sig ha en mer aggressiv tumör i operationspreparatet. Vi analyserade fall mellan 2003–2012. Under studieperioden opererades i hög grad även män med lågrisk prostatacancer. Vi fann 6 638 män som opererats där vi hade tillgång till pre- och postoperativa tumördata. Av dess hade 1,696 (26%) män förstagradssläktingar som tidigare diagnosticerats med prostatacancer. Vi kunde inte finna att män med förstagradssläktingar hade högre risk att bära på en mer aggressiv än andra män som opererades. Slutsatsen blev att behandlingsrekommendationen till män med lågrisk prostatacancer inte ska ändras enkom utifrån att patienten har en förstagradssläkting med prostatacancer.

I **delarbete 4** analyseras förekomsten av mutationen HOXB13 G84 och dess relation till kliniskt betydelsefull prostatacancer bland män 50–69 år. Studiedeltagarna bjöds in till en screeningstudie i Stockholm 2012–2015. Genen för HOXB13 producerar ett protein som förhindrar utveckling av tumörceller. Mutationen HOXB13 G84E inaktiverar proteinets normala funktion. Det är känt från tidigare studier att bärarskap av HOXB13 G84E ger ökad risk för prostatacancer men inte om det är associerat till sjukdom av klinisk betydelse. Vi fann att män som är bärare av HOXB13 GE84 löper cirka dubbelt så högre risk att drabbas av kliniskt betydelsefull prostatacancer. En delförklaring kan vara att HOXB13 G84E driver upp PSA-värdet så att dessa patienter biopseras i högre utsträckning.

ABSTRACT

Background: Prostate Cancer (PCa) is the second most common malignancy among men in the world. In Sweden about 10,000 new cases are diagnosed each year. Mortality rates have been rather stable but have declined the past decades due to early diagnosis and treatment at the expense of overtreatment. High age, ethnic origin and family history are known risk factors. The strongest predictor for poor prognosis is tumour differentiation at diagnosis. Previous studies have suggested that men with family history of mortal PCa, themselves are at higher risk for mortal disease. In twin studies it has been demonstrated that the contribution of shared genome to PCa risk is substantial.

Aims: The overall aim is to explore the importance of family history as a prognostic marker for prognosis in PCa. Specifically, in *Paper I*: To estimate the concordance of tumour differentiation among pairs of brothers with PCa. *Paper II*: To estimate the relative differences in risk of non-low PCa between different types of brothers. *Paper III*: To estimate if men with family history of PCa have higher risk of postoperative histopathological upgrading or upstaging comparted to men without family history. *Paper IV*: To evaluate the prognostic value of the HOXB13 G84E mutation in a screening cohort.

Methods: PCBaSe provides a population-based database with the National Prostate Register (NPCR) linked to several other National registers in Sweden. In *Paper I* 1,022 pairs of brothers with PCa diagnosed 1996-2006 were identified. The relative risk for the second brother to be concordant in tumour differentiation (Gleason score) was estimated with SIR. In *Paper II* 4,262 pairs of brothers with PCa diagnosed 1996-2012 were identified. Using the Swedish twin register and the Multi-Generation Register, all pairs of brothers were stratified by type of fraternity. Tumour characteristics were compared and the risk of concordance for non-low risk PCa was estimated. In *Paper III*, 6,638 men with low risk PCa treated with prostatectomy 2003-2012 were identified. Of those, 1,696 (26%) had family history of PCa among FDRs. The excess risk of postoperative upgrading or upstaging was estimated using logistic regression comparing men with and without family history of PCa. In *Paper IV* the study population was based on a screening cohort in Stockholm County 2012-2015. 27,578 men with Prostate Specific Antigen (PSA) >1 were offered genetic testing with 232 Single Nucleotide Polymorphisms (SNPs) associated with PCa. Men with PSA>3 were offered biopsies. Carriers of HOXB13 G84E were compared to non-carriers for risk of significant PCa.

Results: In *Paper I,* we found an overall risk of concordance in tumour differentiation of SIR 3.1 (95% CI, 2.9–3.3). SIR for brothers of men with high grade Gleason score was 4.00 (95% CI, 2.63–5.82). In *Paper II,* the adjusted OR for concordance in non-low risk PCa among monozygotic twins was 3.85 (95% CI, 0.99-16.72) and for full brothers adjusted OR was 1.21 (95% CI, 1.04-1.39). In analyses restricted to pairs of brothers diagnosed within 4 years, the

results were similar. In *Paper III,* the risk of postoperative upstaging among men with first-degree relatives (FDR's) with high grade or lethal PCa was OR 1.06 (95% CI, 0.76-1.47). For risk of upgrading, OR was 1.17 (95% CI, 0.91-1.50). In Paper IV, the prevalence of HOXB13 G84E was 1.3% of 27,578 men with PSA between 1 and 100. The overall risk of any cancer for HOXB13 G84E carriers was OR 4.67 (95% CI, 2.93-7.73). The risk for clinically significant cancer was OR 2.10 (95% CI, 1.34-3.26).

Conclusions: Men with brothers with high grade PCa are at higher risk themselves for high grade PCa, which have an impact on counselling these men. Shared genetic factors seem to increase the risk of non-low risk PCa. The highest increase in risk is observed among monozygotic twins, although with non-significant estimate. Men with familial history of high risk or lethal PCa are not at higher risk of postoperative upstaging or upgrading after prostatectomy for low risk PCa, compared to men without family history. Those men can comfortable be recommended active surveillance on the same basis as men without family history. Carriers of the rare HOXB13 G84E mutation are increased risk for clinically significant and HOXB13 G84E and we argue that HOXB13 G84E should be included for men recommended genetic counselling.

LIST OF SCIENTIFIC PAPERS

I. **Concordance of tumor differentiation among brothers with prostate cancer -** Jansson KF, Akre O, Garmo H, Bill-Axelson A, Adolfsson J, Stattin P, Bratt O
EUROPEAN UROLOGY 62 (2012) 656–661

II. **Concordance of Non-Low-Risk Disease Among Pairs of Brothers With Prostate Cancer** - Jansson F, Drevin L, Frisell T, Stattin P, Bratt O, Akre O
Journal of Clinical Oncology 36:1847-1852. 2018

III. **Risk of Postoperative Upstaging or Upgrading Among Men with Low-Risk Familial Prostate Cancer** - Jansson F, Folkvaljon F, Stattin P, Bratt O, Akre O
The journal of urology, 2020, Vol.204(1), p.79-81

IV. **Prevalence of HOXB13 G84E mutation and its association to prostate cancer in a population-based screening cohort** - Jansson F, Eklund M, Akre O, Aly M, Egevad L, Wiklund F, Grönberg H, Nordström T
(manuscript)

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LIST OF ABBREVIATIONS

CI	Confidence Interval
FDR	First-degree Relative
HR	Hazard Ratio
ISUP	International Society of Urological Pathology
MGR	Multi-generation Register
NPCR	National Prostate Cancer Register
OR	Odds Ratio
PIN	Personal ID number
PCa	Prostate Cancer
PCBaSe	Prostate Cancer Database Sweden
PSA	Prostate Specific Antigen
RP	Radical Prostatectomy
RT	Radiotherapy
SCR	Swedish Cancer Register
SNP	Single Nucleotide Polymorphism
STR	The Swedish Twin Register

1 BACKGROUND

1.1 EPIDEMIOLOGY

Being the second most common malignancy among men after lung cancer, prostate cancer accounts for about 14% of cancer cases worldwide. By region, prostate cancer is the most common malignancy in Europe, North- and South America, Oceania and Africa (except Northern Africa). The highest incidence numbers are observed in North America, Western Europe, the Nordic countries, Australia and New Zealand. Lowest incidence numbers are observed in Asia[2].

Prostate cancer usually affects men late in life. As average age in many populations increase the incidence of prostate cancer is rising. Advances in treatment of competing risks, such as vascular and heart diseases, contribute to survival of more men that reach the age where prostate cancer becomes a health problem.

The incidence of prostate cancer remained stable until the 1990' when PSA was introduced. In the US, incidence numbers then increased rapidly. The same pattern was observed in other countries, but with an offset of a few years. In Sweden, the increase was observed around 1997(Figure 1.1). During the last decade, though, we see a decreasing trend in incidence, probably explained by the insight of not treating indolent tumours and the concept of active surveillance. Incidence numbers are largely reflected by the level of income. In high-income countries with advanced healthcare systems, diagnostic activity is high leading to the detection of prostate cancer in early stages. (Figure 1.1, Figure 1.2)

Following the high incidence numbers, prostate cancer is a common cause of cancer-specific mortality but demonstrates less variation worldwide. In Sub-Saharan countries the mortality rates are notably high in contrast to the relatively low incidence rates. The same is observed for population of African descent in for example, North America and the Caribbean (Figure 1.1, Figure 1.2).

Figure 1.1. Trends in incidence and mortality exemplified in 6 countries

Prostate cancer incidence and mortality
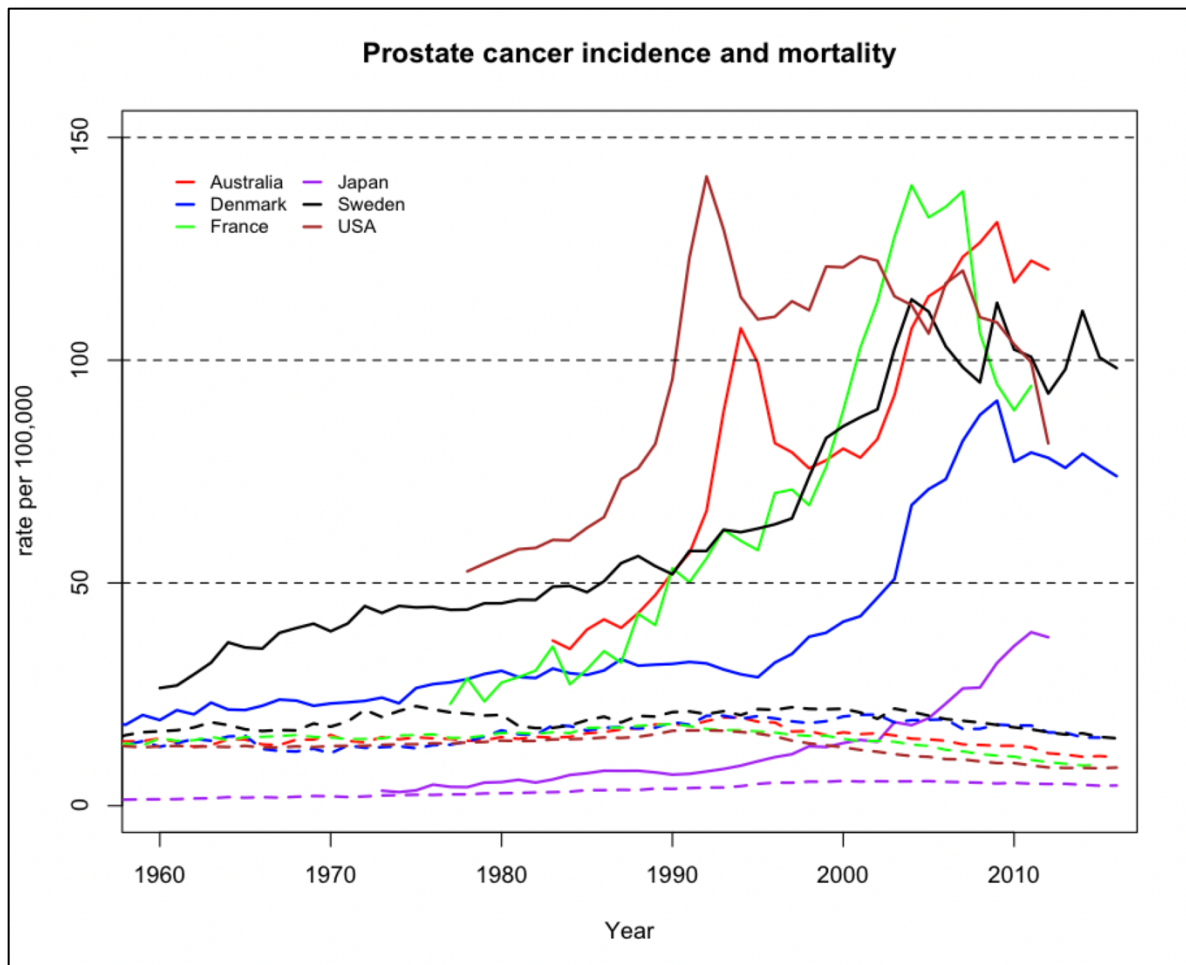
Data from IARC, WHO

Despite early treatment with curative intention, no dramatic effects on disease-specific mortality have been observed. From around 2003 mortality rates have slightly decreased. The reason for this is that many cancers are high differentiated tumours with low mortal potential. The consequence is widespread overtreatment and subsequent morbidity and mortality related to complications from treatment. Large randomized trials have demonstrated reduced mortality with structured screening programs, but with the disadvantage of overdiagnosing and overtreatment of indolent tumours[3]. Worldwide, only a few public health organizations have advocated for the introduction of public screening programs[4].

Figure 1.2. World mortality rates in prostate cancer, all ages. Age standardized (World)
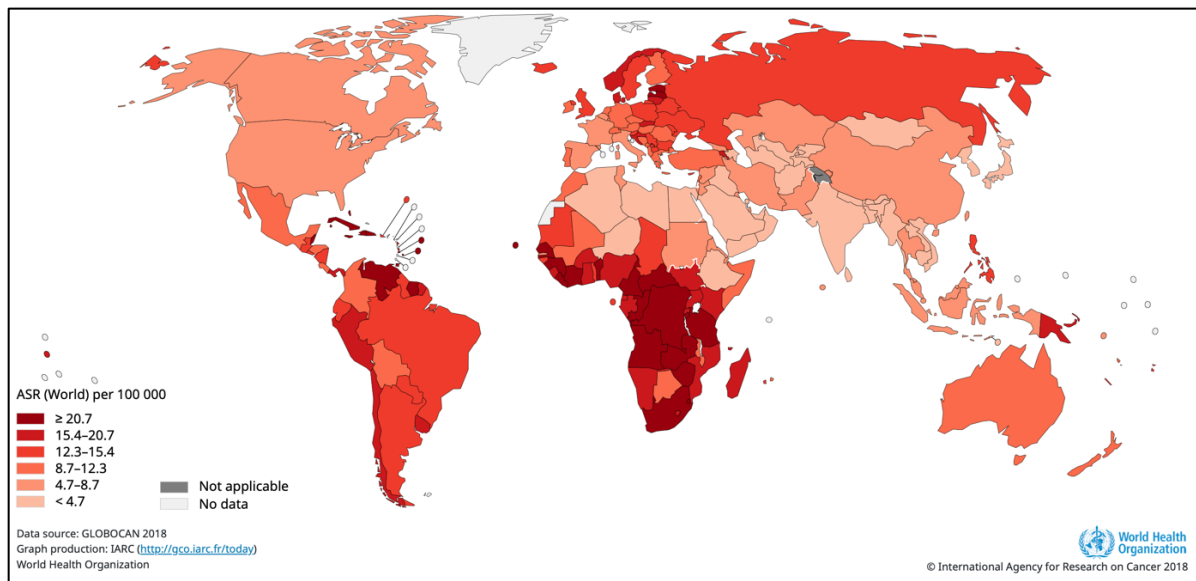
Data from IARC, WHO

The exact aetiology for prostate cancer is not known. Important risk factors are high age, ethnic origin and family history. Although prostate cancer is dependent on androgens via the androgen receptor, physiologic circulating levels of androgen have not proved to be independent risk factors[5]. Overweight and hormonal factors such IGF-1 has a positive, yet complex, association[6]. Lifestyle risk factors are probably important and many factors with weak association have been found[7]. For decades, researchers have also tried to establish an infectious pathway to disease. Common human pathogens, such as human papillomaviruses, Epstein-Barr virus, cytomegalovirus and herpes simplex virus have all been assessed but no causal connection have been found[8]. The most reasonable approach is to consider prostate cancer, like many other diseases, as multi-factorial.

1.2 PROGNOSTIC FACTORS

1.2.1 Gleason score and ISUP

Gleason score expresses the pathologic pattern for tumour differentiation in prostate cancer. DF Gleason invented the system in 1966. In his original work, the grading system was based on 270 cases of prostate cancer[9]. The pattern is based on gland-specific features by how they present in the microscope. A score of 1-5 is given, where 5 is the most malignant pattern. Two numbers compose the Gleason score. Originally, they represented the two most abundant patterns, for example 4+3=7. The Gleason score ranges from 2-10. Today, Gleason score of 5 or less is not considered as cancer. In recent years, considerable effort has been made to standardize how pathologists interpret the biopsy slides. In studies comparing Gleason score in needle biopsy specimen with radical prostatectomy specimen it was evident that many tumours were upgraded. In 2005, at the International Society of Urological Pathology (ISUP) meeting[10] the common practice was changed. The most important being that specimen with cribriform glands now were classified as pattern 4 instead of 3 and that the most malignant pattern should always be reflected in the Gleason score. In clinical practice, it meant that more tumours were graded with a pattern 4 component than before. The proportion of intermediate differentiated tumours apparently increased, leading to a stage migration. This is something to take into account when analysing register data and it might affect the estimates.

At the ISUP meeting in 2014 it was decided to advocate for a new grading system[11]. The new system is based on 5 grade groups, were 5 is the most malignant. Grade group 1 will correspond to Gleason score 6 (Table 1.1). As of 2016, WHO has accepted the new grading system that probably will phase out Gleason score in the future.

Table 1.1. International Society of Urological Pathology 2014 grades

Gleason score	ISUP grade
2–6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4, 3+5, 5+3)	4
9–10	5

Tumour differentiation is the single most important predictor of poor prognosis in PCa[12,13]. In a study by Akre et al. [14], the mortality rates were compared for men with localized prostate cancer, treated conservatively. The overall Gleason score-specific cumulative mortality was 28% for GS 2-6, increasing to 64% for GS 9-10 at 8 years of follow-up (Figure 1.3). The proportion of cancer-specific mortality compared to other causes of death, decreased in older age groups reflecting the influence of competing risks.

Figure 1.3. Cumulative mortality from prostate cancer and other causes after diagnosis of locally advanced prostate cancer, stratified by age and Gleason score
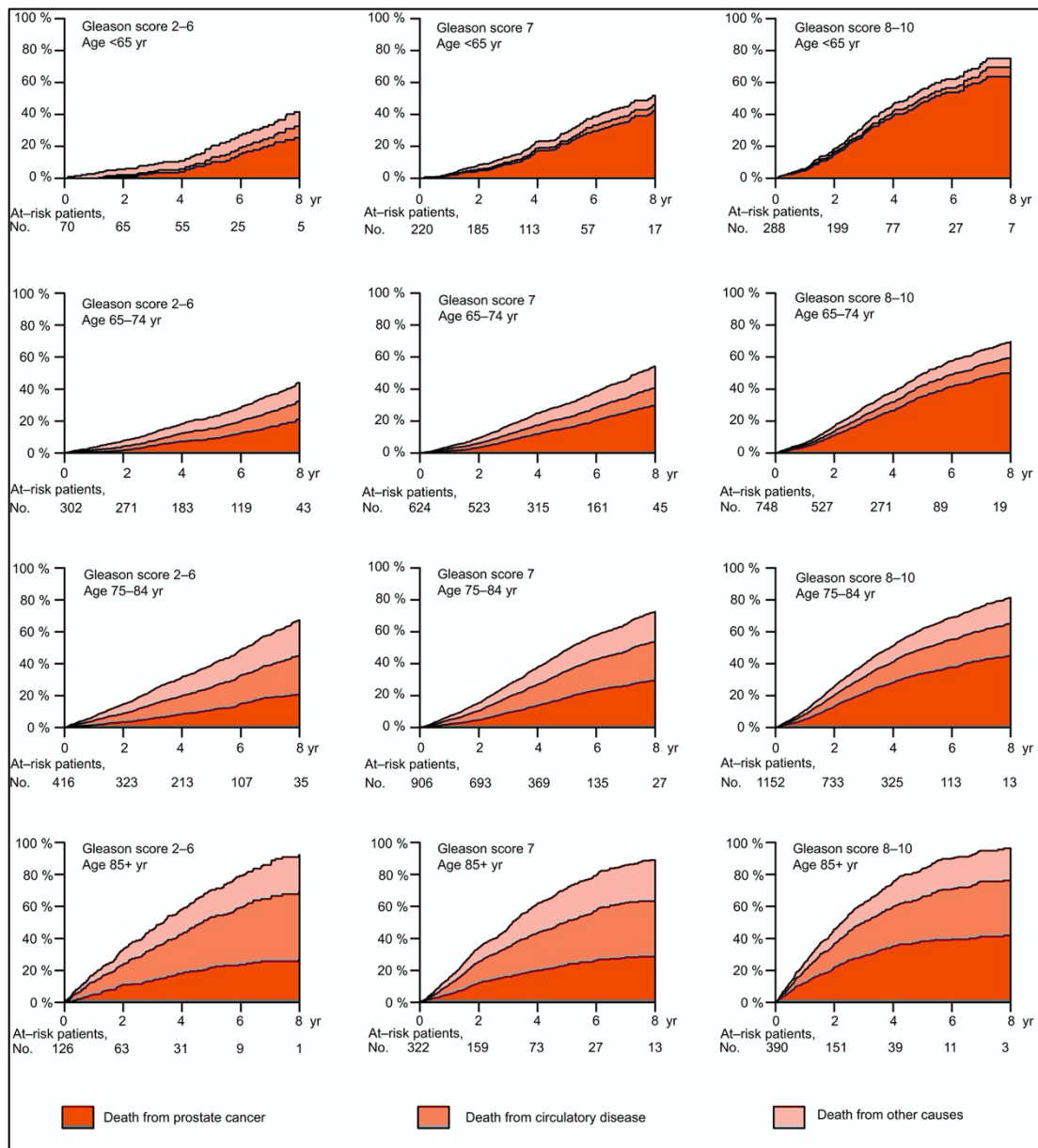
Akre, Eur Urol 2011

1.2.2 Prostate-specific antigen (PSA)

PSA is a glycoprotein synthesized specifically in the epithelial cells of the glands of the prostate. Physiologically, PSA is secreted in the semen and helps sperms through the passage of the cervix channel. Normally, the level of PSA in blood is low. However, under conditions when the prostate is affected by pathological or physiological events, PSA leaks into the blood path. Infections, prostatic hyperplasia and prostate cancer all lead to elevated levels of PSA. Diagnostic procedures such as, biopsy of the prostate and cystoscopy may increase levels of PSA. Even after ejaculation, a transient peak in PSA level may occur. Digital rectal exam (DRE) is not considered to increase PSA-levels.

The introduction of PSA testing in the 1980's gave the possibility to diagnose prostate cancer long before symptoms of the disease are evident. PSA is one of the most sensitive biomarkers for a cancer disease known within medical science. It is no understatement to say that testing for PSA has revolutionized prostate cancer diagnostics. Despite that, its role as prognostic marker is vague. According to the widely used D'Amico classification[15], PSA levels <10 ng/ml is associated with low risk cancer, 10≤19.9 with intermediate risk and ≥20 with high risk. The prognostic value is strong for ISUP ≤2. For higher ISUP grades, the independent prognostic value for PSA decreases due to the increasing proportion of poorly differentiated tumours producing low levels of PSA[14].

Since specificity for PCa is low, the medical history, comorbidities and physical exam must be taken into account when interpreting the result of a PSA test.

1.2.3 Stage

Staging of prostate cancer is assessed with a combination of clinical examination and various imaging techniques. DRE (Digital Rectal Exam) is considered gold standard but has limited sensitivity and specificity[16]. Ultrasound is routinely only used for guidance of biopsies. Computed tomography (CT) has low sensitivity for lymph node detection, especially for low risk disease. It may be used to assess the presence of bone metastasis alongside bone scintigraphy. Magnetic Resonance Imaging (MRI) has high sensitivity (>90%) for ISUP≥2 tumours when interpreted by dedicated radiologists, but specificity is still low (~35%). Yet. reproducibility is improving over time since the PIRADS scoring system was launched[17]. In recent years, the use of MRI and PET/CT has been established for staging of lymph nodes and distant metastasis of high-risk tumours. The role in treatment of these techniques is yet to be determined and several RCTs are ongoing[18]. As for other cancer forms, prostate cancer staging conforms to the TNM classification[19].

Table 1.2. TNM classification for Prostate cancer

T - Primary Tumour (stage based on digital rectal examination [DRE] only)
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically inapparent tumour that is not palpable
T1a Tumour incidental histological finding in 5% or less of tissue resected
T1b Tumour incidental histological finding in more than 5% of tissue resected
T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2 Tumour that is palpable and confined within the prostate
T2a Tumour involves one half of one lobe or less
T2b Tumour involves more than half of one lobe, but not both lobes
T2c Tumour involves both lobes
T3 Tumour extends through the prostatic capsule
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional (pelvic) Lymph Nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M - Distant Metastasis
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

The border between clinical stage T2 (cT2) and T3 (cT3) marks where the tumour extends into surrounding tissue. The prognostic value of tumour stage has been studied extensively. cT3 represents a more advanced tumour compared to cT2 and all cT3 tumours are grouped as high risk disease, regardless of ISUP grade or PSA. In one of the largest follow-up studies after radical prostatectomy, Ward et al compared survival rates of cT3 versus cT2[20].

Table 1.3. Survival rates of cT3 vs. cT2 at 10 and 15 years

Clinical stage	10 yr follow up	15 yr follow up
cT2	96%	92%
cT3	90%	79%

Ward et al. BJU Int 2005

Men with cT3 were more likely to have ISUP≥2, positive margin at surgery and nondiploid chromatin content in the postoperative specimen. Preoperative PSA had no impact on survival in this study.

1.2.4 Risk groups

For prediction and recommendation on treatment, all diagnosed cases are grouped according to risk profile where prognostic factors are taken into account. For localized prostate cancer the stratification into risk groups according to, or derived from, D'Amico et al. [21] is commonly used by leading guidelines[22-24]. Levels of PSA, Gleason score/ISUP and clinical stage define the different risk levels. The risk group stratification was originally developed from a selected cohort and the endpoint of D'Amico's study was biochemical recurrence (PSA) after radical prostatectomy (RP) or radiotherapy (RT), not disease-specific mortality.

Table 1.4. Risk stratification groups according to D'Amico et al.

Risk group	Definition
Low risk	cT1-cT2a and GS ≤ 6 and PSA < 10
Intermediate risk	cT2b or GS = 7 or PSA 10 ≤ 20
High risk	≥cT2c or GS ≥ 8 or PSA > 20

Despite its widespread use within the research field, the D'Amico classification harbours many drawbacks. It does not take into account the extent of PCa in the biopsy cores. The definition of the intermediate group is troublesome due to the heterogenic biologic nature of the tumours. A man with extensive ISUP-grade 3 in 12 out of 12 core biopsies and PSA 18, is classified in the same risk group as a man with limited ISUP 2 in 1 out of 12 core biopsies and PSA 6. In the NCCN guidelines[24] two more risk level groups have been added. The D'Amico low risk group is divided into 'Low' and 'Very low' risk group. The latter restricts the stage to T1c, ≤2 positive cores with ≤50% cancer in each core and PSA-density <0.15 ng/mL/g. The intermediate group have been subdivided into 'Favorable intermediate' and 'Unfavorable intermediate' risk categories. The difference between the two categories follows the distinction as for ISUP grade groups 2 and 3, number of positive biopsy cores and if more than one intermediate risk factor is present or not (Table 1.5). In terms of treatment, men with 'Favorable intermediate' may be considered for active surveillance if otherwise suitable, whereas men with 'Unfavorable disease' always are recommended treatment if life expectancy is ≥10 years. In both categories observation and symptomatic treatment is preferred for men with life expectancy ≤10 years. The NCCN guidelines also makes distinction between patients with high risk disease into 'High' and 'Very high' risk groups. Stage T3b-T4, >4 cores ISUP grade 4-5 (or primary Gleason 5 pattern) and more than one high risk feature qualify for the 'Very high' risk category.

Table 1.5. Intermediate risk group as defined in the NCCN guidelines

Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive[e]

The national health group of prostate cancer in Sweden have adopted a similar definition for tumours with very low risk of progression to metastatic disease[25]. The criteria for the very

low-risk category is: T1c, <8 mm cancer in ≤4 of 8-12 biopsy cores. PSA-density < 0.15 µg/l/cm^3.

Other tools for risk prediction are the Cambridge Prognostic Groups (CPG) [26],[27] the Cancer of the Prostate Risk Assessment (CAPRA) [28] score and the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram[29]. In a recent study by Zelic et al. the performance of the different prediction tools was compared head-to-head on population-based data in PCBaSe. They concluded that all three prediction tools mentioned above performed better than the D'Amico derived risk systems in predicting prostate cancer mortality[30]. When predicting risk of PCa-specific mortality with MKSCC nomogram, the D'Amico risk groups are overlapping (Figure 1.4). For the D'Amico high risk group, the risk of dying within 15 years after diagnosis, ranges from ~3% to ~54%. Even if the D'Amico risk groups may seem well separated, the wide range makes prediction for the individual patient challenging when using the D'Amico risk groups.

Figure 1.4. MSKCC vs. D'Amico
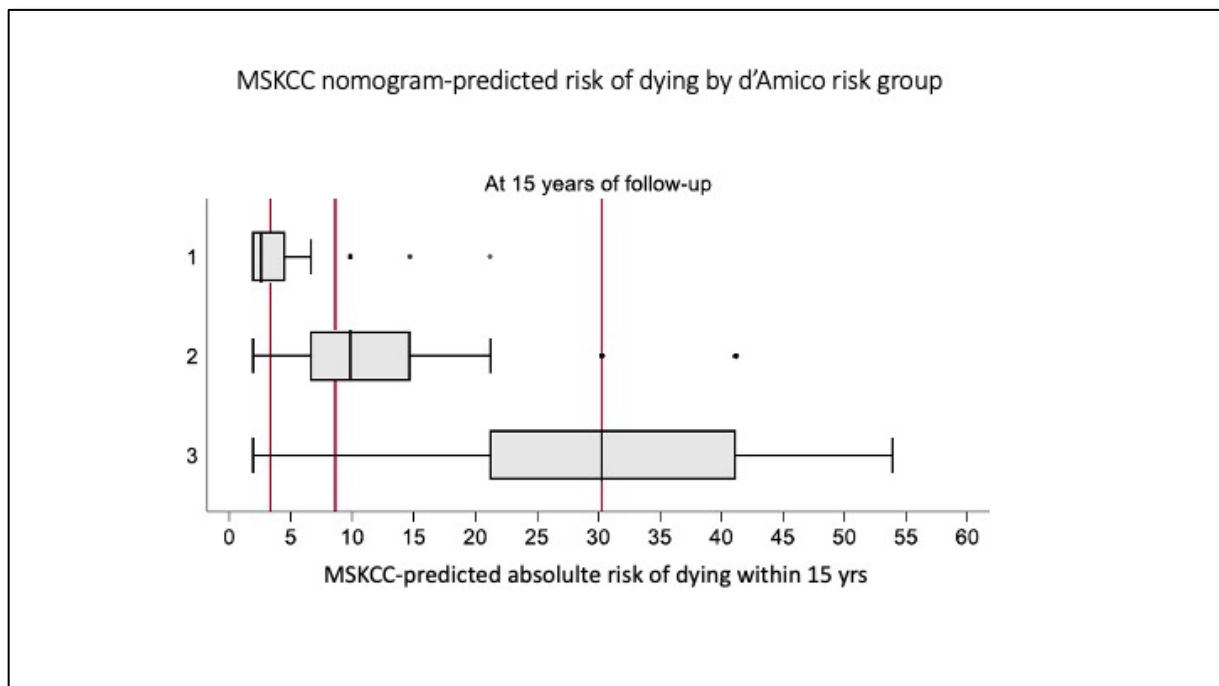
Zelic et al., Eur Urol 2020

1.3   FAMILIAL OCCURRENCE

Familial history of any disease is important when assessing the risk of healthy family members to be diagnosed. For most sporadic cancer the pattern is not evident and the contribution from genes with low penetrance and shared environmental factors are rarely known. Twin studies

may be used to estimate the relative contribution from shared genes and environmental factors[31]. Shared genes may be confined to a single mutation in a single gene, complex variants of a specific gene or a combination of variants in many genes, yielding a higher risk of tumour development. Some genetic syndromes, such as von Hippel-Lindau (angioblastomas, renal cell carcinomas, pheochromocytoma and endocrine pancreatic tumours) [32], Lynch syndrome (colon cancer, endometrial cancer, upper tract urothelial cancer and potentially PCa) [33] or MEN 1 & 2 (multiple endocrine neoplasia of thyroid, parathyroid and endocrine pancreas) [34,35] increases the risk for different tumour forms. Other syndromes are linked to specific tumours. In FAP (Familial Adenomatous Polyposis) a mutation of the APC gene causes colon cancer[36].

A history of prostate cancer within the family is known to be one of the strongest risk factors for prostate cancer. The first case-report of monozygotic twins with PCa is dated 1960. During 1980s', Miekle et al. investigated familial aggregates of PCa in the Utah Mormon population[37]. They found a 4-folded increased risk of PCa among brothers of probands. Since then, many studies have revealed a 2 to 5-folded increased risk for first-degree relatives[38]. The risk is even considerable for 2nd – and 3rd degree relatives to men with prostate cancer[39]. By convention, a case of prostate cancer is inherited if it fulfils one of the following conditions[40]

- Three or more relatives with prostate cancer.

- Two or more relatives with early onset prostate cancer, i.e. before age 55.

For research purposes a more flexible definition of familial aggregates of prostate cancer is needed. The term 'Familial prostate cancer' is used by many authors but has no unambiguous definition.

1.4 GENETICS

Register-based twin studies from the late 1990' established that genetic factors are of importance in familial prostate cancer. Grönberg et al found 16 monozygotic (MZ) and 6 dizygotic (DZ) twin pairs diagnosed between 1959 and 1989 using the Swedish Twin register[41]. Page et al found concordance among 57/17 (MZ/DZ) twin pairs in the NAS-NRC Twin Registry[42].

Heritability is defined as the proportion of variance in phenotype explained by variance of genotype. Monozygotic twins share virtually 100% genes and dizygotic twins share, on average, 50% genes.

The model used for estimates on heritability is based on the theory of additive genetic effects[43]. The contribution of variance to a specific trait can be pure genetic, environmental or

an interaction of both environmental and genetic factors. Further, quantitative genetic analyses for twin studies usually make assumptions of shared environment for MZ and DZ twins, no interaction between genetic and environmental factors and that random mating occurred. Two studies with data from Nordic twin registers, have estimated heritability for prostate cancer[44,45]. The twin study by Lichtenstein et al investigated the concordance of many cancer types with combined data from the Swedish, Finnish and Danish twin cohorts. The strongest associations were found for breast, colorectal and prostate cancer that is the three major types of cancer. Heritability was estimated to 42% from 40/20 (MZ/DZ) concordant twin pairs. Based on this knowledge, Hjelmborg et al, investigated prostate cancer further. The Norwegian twin cohort was added and the heritability estimates for prostate cancer were reassessed giving 58% explained by hereditary factors in 194/146 (MZ/DZ) twin pairs.

The two studies mentioned above, inspired Paper II. Most studies in the field have focused on concordance in the diagnosis of PCa within families, whereas paper II in this thesis undertakes the aspect of heritability and concordance in prognosis between different types of brothers.

Genetic knowledge is a fast-growing field and a complete overview is far beyond the scope of this thesis. Genetic profiling will probably become standard procedure in diagnostic and prognostic evaluation of PCa in the future.

Many candidate genes have been found through GWAS studies[46,47]. Some have shown promising results and are under evaluation[48] but have yet to prove their clinical importance. A few medium to high penetrant genes and SNPs, such as BRCA1, BRCA2 and HOXB13 G84E, have rendered deeper interest and are described below. Most oncogenes play a role in different cancer forms. Prevalence of oncogenic mutation differs between populations. Most genetic studies are conducted on cancer patients or families to cancer patients. The knowledge of prevalence in general unselected populations is there for scarce.

1.4.1 Single nucleotide polymorphism - SNP

An SNP is a single point in the genome where there may be variability (point mutation) between individuals. If the SNP is located in the coding part (exon) of the gene, some forms may cause or increase the risk for diseases. Each gene consists of thousands of SNPs. To date, >280 susceptible loci[49] have been recognized and linked to prostate cancer risk, prognosis and prediction. Most SNPs found in GWAS studies are low-to-medium penetrant, but the multiplicative effect from many SNPs may result in an overall increase in risk for disease. Associated SNPs are referred in studies by either the SNP Id or the harbouring gene. Some oncogenes have several associated SNPs within the exon. Even if relatively strong associations have been found for a few SNPs, their clinical importance is less explored. An exception is HOXB13 G84E (Table 1.6). A review by Benafif et al. summoned all SNPs found through GWAS studies with estimated association to PCa expressed as odds ratios[50].

Table 1.6. 10 SNPs with strongest association to PCa found in GWAS studies

SNP Id	Chromosome	Alleles	OR	Comment
rs138213197	17	T	3,85	HOXB13 G84E
rs183373024	8	G	2,91	Associated to gene MYC
rs78554043	22	C	1,62	Gene CHEK2
rs16901979	8	A	1,56	Associated to gene MYC
rs75823044	13	T	1,55	Found in African populations
rs1447295	8	A	1,41	Gene CASC8
rs7210100	17	A	1,34	Gene ZNF652
rs138466039	11	T/C	1,32	Gene PKNOX2
rs76551843	5	A/G	1,31	Gene DOCK2
rs138004030	6	G/A	1,27	Associated with early onset

Benafif, Can Epi Bio Prev 2018

There are companies offering genetic testing with SNP-panels. The tests typically test for 10-16 SNPs with the strongest association to PCa. A recent list of available SNP-tests was published by Heidegger et al[51].

1.4.2 HOXB13 G84E

The HOXB13 gene produces a protein which act as a transcription factor and thus regulates the expression of other genes. It also has a role as tumour suppressor. The specific variant (SNP) of interest is G84E. This variant is rare, and prevalence is 0.1-1.5% in European populations and lower in African and Asian populations[52,53].

Most previous studies have reported relative risk for any PCa among carriers of HOXB13 G84E compared to controls. In a recent meta-analysis, Nyberg et al reported a pooled estimate of RR 3.43 (95% CI, 2.78–4.23) from 17 unselected case-control studies (relative risk range: 0.95-14.70) [53]. Storebjerg et al. reported a correlation for HOXB13 G84E to aggressive disease when analysing post-operative specimen. Gleason ≥7 (ISUP 2-5) was found in 61% of non-carriers and in 83% of HOXB13 G84E carriers[54].

In paper IV, prevalence of HOXB13 G84E and association to significant prostate cancer is described in a screening cohort.

1.4.3 BRCA1 & BRCA2

BRCA1 and BRCA2 are tumour suppressor genes and was originally associated with breast and ovarian cancer risk[55]. The genes code for proteins that aid in repairing damaged DNA and subsequentially prevent the cell from transforming into tumour cell. More than 2,000 different mutations have been found[56]. Many of them result in oncogenetic transformation of the transcribed protein. The association to PCa is less extensively explored.

Results from studies of families with mutation carriers show a 2 to 6-folded risk of PCa, especially at younger age (<65 yr.) and an association with aggressive disease for BRCA2 has been proposed. For BRCA1, the risk is 0.3 to 4-folded and the association with aggressive PCa is even less clear[57].

Association to increased risk of PCa has also been found for men with family history of breast cancer in general[58].

1.4.4 ATM

The ATM gene codes for a protein involved in DNA repair and co-operates with the BRCA1 protein[59]. Mutations in the ATM-gene are related to prostate cancer, breast cancer, melanoma.

1.4.5 CHEK2

The CHEK2 is a tumour suppressor gene linked to ATM. Closest related cancer forms are: Breast cancer, ovarian cancer, colorectal cancer, thyroid cancer, germ cell cancer and renal cell cancer[60-62].

1.4.6 Lynch syndrome - MLH1, MSH2, MSH6, and PMS2

These genes function in the repair system following DNA damage. Any mutation causes the Lynch syndrome which is closely related to colon cancer and upper tract urothelial cancers. Evidence is growing for moderate increased risk for prostate cancer[63,64].

1.4.7 Summary of prostate cancer risk-genes

Table 1.7. Summary of selected prostate cancer associated genes

Gene	Estimated increase in RR	Aggressive disease
BRCA1	1.8 – 3.8	No
BRCA2	2.5 – 4.6 8 - 23 for <55 yr.	Yes
HOXB13 G84E	3.4 – 8.6	Yes*
ATM	6.3	Yes
CHEK2	1.9 – 3.3	No
Lynch syndrome	3.7	No

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* = In study 4 of this thesis we argue that HOXB13 G84E is associated with significant prostate cancer.

1.5 CURRENT TREATMENT

Detailed description of treatment and treatment decisions is not covered here. A brief overview is given for understanding why there is a need for better prognostic markers.

Treatment intention can be curative, palliative or conservative.

Curative treatment is considered in men with no or moderate co-morbidities, no evidence of metastatic disease and have a life expectancy of at least 10- to 15 years. Surgery, i.e. radical

prostatectomy, is performed either as a laparoscopic (usually robot-assisted) or open procedure. The prostate is completely removed and an anastomosis between the bladder and urethra is established. Besides short-term complications such as bleeding and infection, the procedure is afflicted with urinary leakage and impotence. According to a systematic review by Ficarra et al., urinary leakage is seen in about 10% of cases and postoperative potency rates are between 50%-90%[65]. Especially for potency, the risk for an individual patient is dependent on pre-operative function of potency, tumour characteristics, surgical skills and choice of nerve-sparing technique. Another modality for curative treatment is radiotherapy. The radiation is delivered to the prostate either as external beam radiotherapy (EBRT) or as brachytherapy. Acute and late side-effects include gastrointestinal and urinary symptoms. Most commonly reported are dysuria, urinary retention, urinary frequency, diarrhoea and rectal and urinary bleeding. Most acute side-effects of radiotherapy resolve within 3-6 months, but for some patients, late and lifelong side-effects are seen[66].

These complications may have substantial influence on quality of life, of which patients must be informed before treatment decision.

To date no randomized trial has demonstrated superiority between radical prostatectomy and radiotherapy in terms of cancer survival.

Palliative treatment is considered for men with symptoms of locally advanced or metastatic disease. Hormone (androgen deprivation) therapy blocks the androgen (testosterone) receptor and reduces tumour burden. For selected patients with metastatic disease, systemic cytostatic therapy may come in question. The field of treatment for metastatic PCa is growing rapidly. Novel agents in standard oncologic treatment are docetaxel, abiraterone and enzalutamide.

Conservative (or Deferred) treatment. Many patients live with prostate cancer for many years, even decades. For the aging patient with asymptomatic disease, conservative treatment is usually the best option. The patients are evaluated clinically and with PSA-test regularly. At progression to metastatic or symptomatic disease, palliative treatment may come in question. This regime is usually referred to by the term W*atchful Waiting*.

A special case of conservative treatment is A*ctive Surveillance (AS)*. The use of PSA has primarily led to the diagnosis of many low risk tumours with ISUP grade 1. Today, if no family history is present and if the patient agrees, these men are recommended AS to reduce the risk of overtreatment of indolent cancer tumours and delay curative treatment.

Active surveillance is an option for men in the very low up to intermediate (with favourable tumour characteristics) [67] risk group who are eligible for curative treatment if progression occurs to significant cancer. The patients are enrolled to a stringent follow up programme with regular PSA-test, clinical exam and repeated biopsies as long as curative treatment is an option for the patient. In a review article of ten AS-studies, progression on re-biopsy was the strongest predictor for discontinuing AS and recommend curative treatment. PSA velocity or doubling

time were not independent predictors for progression but may act as triggers for re-biopsy. Time to re-biopsy ranged from 1 to 3 years. After 5 and 10 year follow up, 14-41% and 40-59% respectively, had discontinued AS. The majority of patient who discontinued underwent curative treatment[68]. The median interval from initial enrolment to discontinuation of AS due to progression, was about 3 years in all reviewed studies. Several studies have revealed a 30-40% risk of upgrading after radical prostatectomy[69,70]. This indicates that many patients are under graded at start of AS rather than that biologic progression of indolent tumours occurs. The role om MRI in AS have been studied, but so far results are not strong enough to replace re-biopsy with MRI[71]. The procedure with prostate biopsies involves a non-negligible risk of serious infection. With annual re-biopsy, as the EAU-guidelines recommends, the accumulated number of patients with infectious complications after biopsy must be considered.

1.6 THE PROGNOSTIC CHALLENGE

Both over- and underdiagnosing is a dilemma within prostate cancer care. Overdiagnosing is associated with over treatment and complications to treatments that could have been avoided. In addition, many men are affected by the burden of carrying the knowledge of having cancer, even if it may never impose a health problem to them. Underdiagnosing of potential lethal tumours deprives men from effective curative treatment.

A novel concept for increasing the specificity for biopsies and maintaining the sensitivity for high-risk prostate cancer was presented in the STHLM3 screening study[72]. The investigators used a genetic score composed of protein and genetic biomarkers that have been associated with prostate cancer. In combination with conventional PSA testing, family history and clinical examination, the number of men recommended for biopsy could be reduced and specificity of diagnosing significant cancer maintained.

Since prediction of prostate cancer seems to depend on a multifaceted set of factors, we will probably see more complex and individualized algorithms to assess prostate cancer risk. In this context, it is essential to assess the relative importance of family history as a prognostic marker.

1.7 FAMILIAL PROGNOSIS

The knowledge of family history, as a risk factor for prostate cancer, is probably diverse among men in general. But if a man is diagnosed with PCa (or any other disease) it is not far-fetched to think that his relatives (especially brothers and/or sons) become concerned about their own risk of PCa. Studies from PCBaSe have shown that the risk for brothers of being diagnosed themselves if markedly increased during the first year after a brother's diagnosis[73]. It is most likely due to behavioural reasons and leads to opportunistic diagnostic activity. When men seek counselling for PCa it would be helpful to have more substantial recommendation than just to

note that there is a family history of PCa. Only increased risk of significant cancer is of clinical interest.

Previous studies on prognosis in familial PCa are mostly based on survival of the fathers. In a large population based study, using the Swedish Cancer Register, Cause of Death register and the Multi-Generation Register, Lindström et al investigated the concordance in survival of the major cancer types (colorectal, breast, prostate and ovarian) within parent-child pairs[74]. The study database included more than 11 million individuals with around 1 million cases of cancer between 1961 and 2001. The concordance was assed using different statistical methods. In the univariable model using the Kaplan-Meier method, the prognosis of the parent was categorized as survivor or non-survivor at 10 years after diagnosis. The children were followed 5 years after diagnosis. The survival was significantly worse for children to parents who did not survive 10 years. In multivariable Cox-models the parent survival was categorized as good, expected and poor. Hazard ratio (HR) was 2.07 (95% CI, 1.13-3.79) for children to parents with poor survival in the fully adjusted model. Further analyses of parent-child pairs with disconcordant cancer sites, found no significant HRs. The results suggested that concordance in cancer type was due to shared genetic or environmental factors. The data did not allow for further estimation of heritability. As the concordance was only observed within each cancer type, it is reasonable to believe that the results were not due to a general vulnerability to cancer. However, concordance between generations are confounded in several ways. Prostate cancer may be a chronic disease for a long period before it leads to death. The 5-year observation period may be too short and thus the concordance may be underestimated. Diagnostic and treatment options have also evolved dramatically during the recent decades and the estimated prognosis at diagnosis is not comparable. Most tumours today are diagnosed in earlier stages in asymptomatic men compared to the generation of their fathers.

Hemminki et al concluded that sons of fathers with survival <24 month after diagnosis had worse outcome in PCa if diagnosed themselves compared to sons with fathers who survived >60 month[75]. Brandt et al published data suggesting increasing PCa specific mortality by number of first-degree relatives (FDR's) with fatal disease. They also saw a trend where familial cases of fatal PCa died at a younger age[76,77].

Current guidelines are not coherent in when a man with family history of PCa should be offered diagnostic evaluation. The EAU guidelines[22] advocate that men from 45 years can be recommended PSA testing, whereas the AUA guidelines[78] recommends offering PSA testing for men 40-54 years if they are at higher risk of PCa, where family history is considered higher risk. When it comes to genetic testing, neither EAU nor AUA have clear recommendations so far. The NCCN guidelines recommend genetic testing for men with 'strong' family history, certain ethnicities or known germline variants, such as, BRCA1&2, HOXB13 or Lynch syndrome.

To address the question of inherited prognosis with an epidemiological approach we need large databases with quality data collected prospectively for long periods. The Swedish national quality registers provide that. With the unique national personal ID number (PIN) several registers can easily be linked to large datasets. The registers are not static, and more parameters are added continuously. Results of genetic testing will probably be included in the future and add valuable information in conjunction with family history for prognostic predictions. To date, knowledge and use of genetic testing is still immature for inclusion in the national registers.

2 AIMS OF THE THESIS

Familial diagnosis in prostate cancer is well explored. The knowledge of how family history impacts prognosis is more scares, but previous findings suggest worse survival outcomes in families with many affected individuals. Today's diagnostic workup with opportunistic screening with PSA and an increasing awareness among men about prostate cancer has led to overdiagnosing of tumours that should have been left undetected. Men with family history of prostate cancer have reasons to be concerned and we need better understanding in how family history affects prognosis to advise those men that benefit from early detection and treatment, without contributing more to overtreatment.

The general aim with this thesis is to explore if there is any prognostic value in family history that can be used in a clinical situation when advising men with prostate cancer. The data used is prospectively collected within various national registers and the population-based Stockholm-3 screening cohort.

Specific aims:

1. Increased relative risk of PCa is well established in FDRs to men with PCa. Whether the risk is increased for sharing tumour differentiation is not known. We aim to evaluate if brothers to men with prostate cancer is at particularly increased risk of prostate cancer with the same tumour differentiation as his proband.
2. To evaluate if prostate cancer among brothers increases specific mortality in prostate cancer in relation to the first brother diagnosed within a family.
3. If concordance in sharing tumour charateristics is attributed to genetic similarity, there may be a dose-response association to the proportion of shared genome among siblings. We aim to describe heritability and concordance in risk groups among different types of brothers with prostate cancer.
4. The risk of adverse pathology after prostatectomy is estimated to 30-40%. If men diagnosed with PCa and FDRs with high risk PCa are at particulary high risk of adverese pathology after prostatectomy is not known. We aim to evaluate if family history changes the risk of postoperative upgrade/upstage of prostate cancer.
5. Carriers of the HOXB13 G84E muation have a 5-10 folded risk PCa diagnosis and it has been suggested that HOXB13 G84E should be included in genetic counseling for men with family history and thus at elevated risk of PCa. We aim to evaluate the relevance of HOXB13 G84E mutation in prognosis of prostate cancer in a population-based screening cohort.

3 METHODS AND MATERIALS

3.1 REGISTERS

The PIN, consisting of date of birth and four numbers is unique to every citizen. The PIN is the unique identifier in all national databases and provides a simple way for linking national databases. For this thesis, relevant databases are briefly described.

3.1.1 Swedish Cancer Register - SCR

The register was established in 1958. It is mandatory for all health providers to report all cancer cases to the register. Cancers are reported by both treating clinician and the pathologist responsible for the histopathological diagnosis. Data quality was insufficient the first years but since then the register is considered to be nearly complete. In a sample study for year 1998, it was concluded that 96% of patients were correctly registered compared to the Hospital Discharge Register. It was concluded that underreporting to the SCR was dependant on tumour site and age. For common cancers, such as breast and prostate, the incidence of underreporting was low but more frequent for some rare forms of cancer[79]. In another study underreporting to the SCR was estimated to 12.5%, compared to the Swedish Register of Palliative Care. The authors concluded the reason may be that elderly patients in some cases have cancer as cause of death based on clinical or radiological findings but not verified with histopathology[80]. The register is administered by The National Board of Health and Welfare (Socialstyrelsen) and is a major resource for science and political decisions for public welfare.

3.1.2 National Prostate Cancer Register - NPCR

The register started as a collaboration among six out of eight regions in Sweden in 1996. From 1998 the register is nationwide[81]. The steering committee includes representatives from all regions. The completeness for NPCR to SCR is about 98% from results of a validating study[82]. Today four separate forms are used for diagnostic data, follow-up, RP and RT. Patients who undergo curative treatment are also asked to fill in extensive questionnaires before and periodically after treatment. In total, more than 400 variables are registered related to diagnosis, tumour characteristics, stage and treatment. NPCR has status of a national quality register.

3.1.3 Multi-Generation Register - MGR

The register contains information on the parents of all individuals registered in Sweden from 1st of January 1961 and were born in 1932 or later[83]. The register is used to identify siblings and children of each index person through the parents. A prerequisite for finding the parents of an index person is that the parents have been registered in Sweden at some point since 1947 when the PINs were introduced. For individuals born in 1935, around 90% of the parents can be

identified. From 1961 the register is virtually complete. A large portion of index persons who died before June 30, 1991 have missing data on their parents. This is due to incomplete transfer of information when the national tax agency took over the responsibility for population registration July 1st, 1991.

3.1.4 The Swedish Twin Register - STR

The register was founded by the end of the 1950s and holds records of twins born in Sweden since 1886[84]. The register includes data of about 87 000 twin pairs[85]. For individuals alive, information is collected through surveys and automatic update from welfare registers.

3.1.5 The Cause of Death Register

The current register was founded in 1961. Historical data is available from 1952-1960. Until 2011 only cases of death among people registered in Sweden were recorded. From 2012, all cases of death within Sweden are recorded regardless if the person is a registered citizen of Sweden or not. The completeness is generally high but in the early years, 1952-1960, some PINs were reused from deceased individuals to immigrants which might affect the quality of data when merged with other registers. Overall, 96% of all deaths have recorded information of underlying causes[86].

In Sweden, since 1991, the tax agency is notified at time of death. The notification does not include cause of death. The full death certificate is reported to the National Board of Health and Welfare within three weeks after death. Until 1991 it was mandatory with a valid full death certificate for burial, with the effect that cause of death registration was close to complete. After 1991 only the notification of death is required. According to a report[87], there is a tendency that the proportion of deaths with missing death certificates is increasing (0.3% in 1995, 0.8% in 2008). A larger proportion of elderly during the last decades, with multiple underlying diseases, is suggested as one of the main reasons. The accuracy of prostate cancer specific deaths was reported in a study by Fall et al. [88]. The official statistics from CDR was compared to medical records of the regional prostate cancer register between 1987 and 2002. They found concordance rates between 83% and 96%. Higher concordance was seen for younger individuals and individuals with localized prostate cancer. There was generally an overreporting of prostate cancer specific deaths in the CDR which seemed to increase over time.

3.1.6 PCBaSe Sweden

To coordinate and simplify register-based research of prostate cancer in Sweden, a linkage between the NPCR and several other national databases was created in 2009[89]. The first version included about 80 000 cases diagnosed between 1996 and 2006 (Figure 3.1). The most recent compilation of PCBaSe Sweden (version 4.0) includes data from approx. 186 000 cases of prostate cancer (Figure 3.2). All data in PCBaSe Sweden are anonymous and the keys to national personal numbers are kept at The Swedish National Board of Health and Welfare.

Figure 3.1. PCBaSe version 1.0
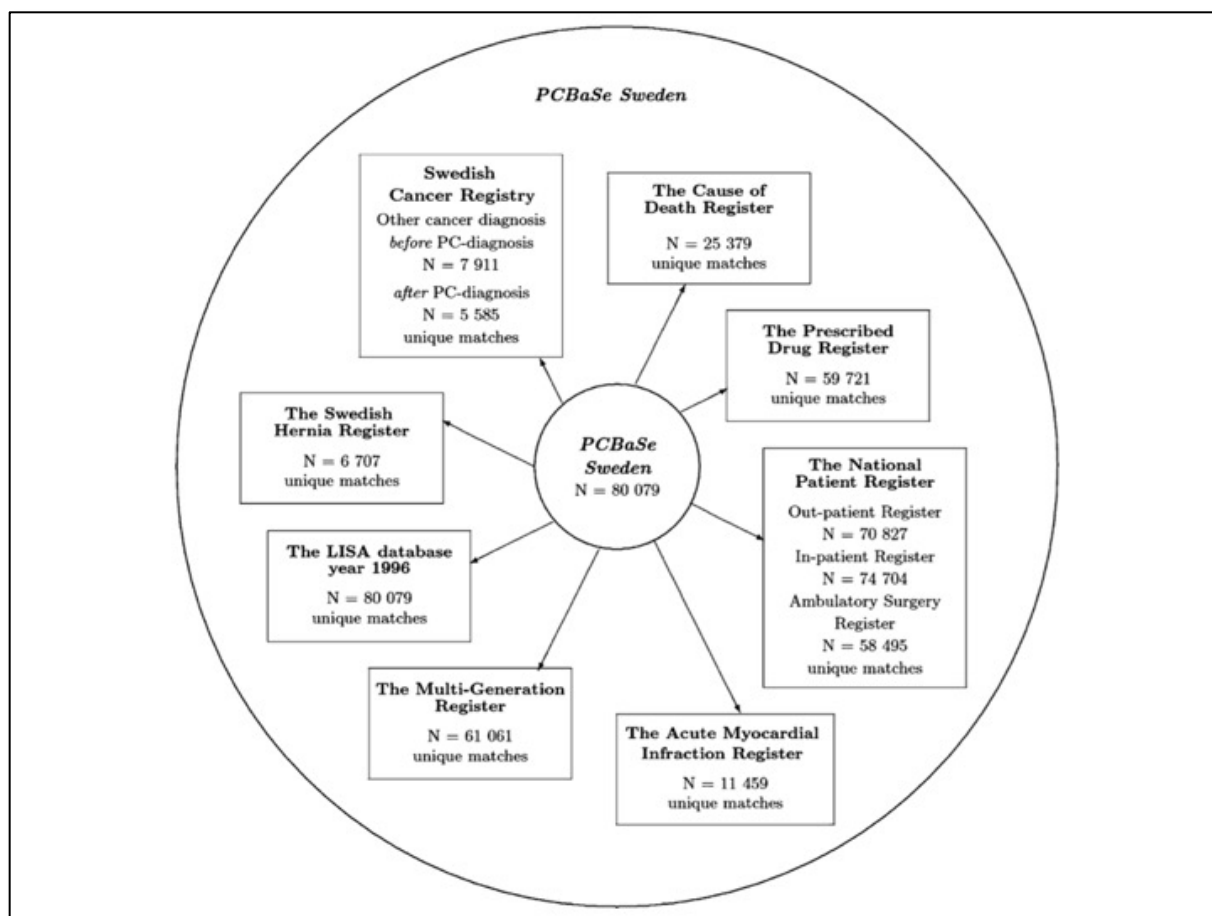
Hagel, Scand J Urol Nephrol 2009

Figure 3.2. PCBaSe version 2.0 - 4.0
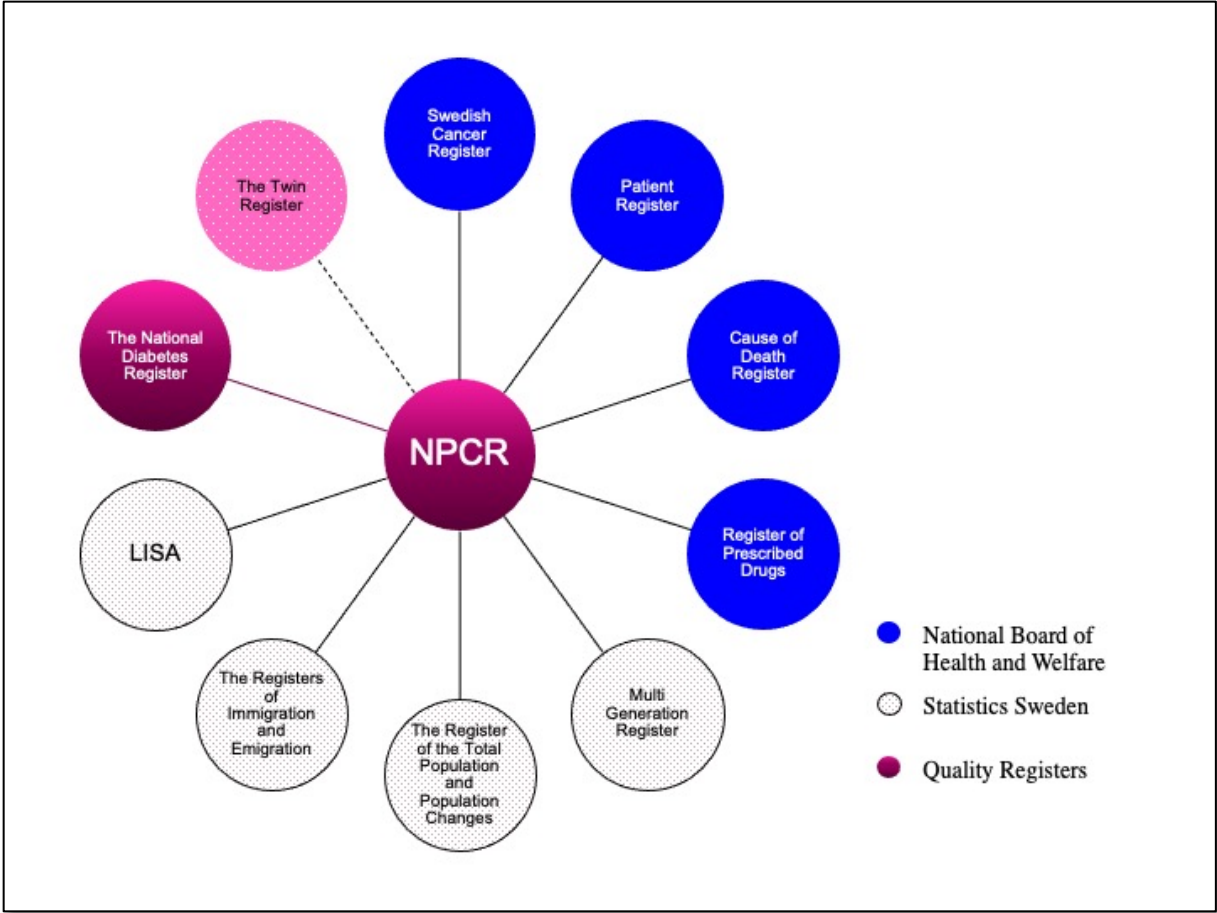
Note: version 3.0 also included the Swedish Twin Register

3.2   OVERVIEW OF STUDY DESIGN AND STUDY POPULATIONS

Table 3.1. Study populations

Study	Data sources	Study population
Paper I	PCBaSe version 1.0 • NPCR • MGR • SCR	1,022 pairs of brothers with PCa, diagnosed 1996-2006
Paper II	PCBaSe version 3.0 • NPCR • MGR • STR	4,262 pairs of brothers with PCa, diagnosed 1996-2012
Paper III	PCBaSe version 3.0 • NPCR • MGR • SCR	6,854 men with low risk PCa, <70 yr., diagnosed 2003-2012, treated with prostatectomy
Paper IV	Stockholm-3	27,578 men with 1≤ PSA ≤100 within the population-based screening programme of the Stockholm3-study, 2012-2015

3.3   STUDY POPULATIONS

In Paper I, data from PCBaSe version 1.0 was used. From the total of 80 079 subjects we identified all their brothers via the MGR. The total numbers of brothers were then linked back to the NPCR to create families of brothers. The first diagnosed brother within a family was considered index case and did not enter the risk set. We identified 21,930 brothers of index cases and followed them up for incidence of prostate cancer. If a brother was diagnosed with PCa in the Swedish Cancer Register prior to 1996 (when NPCR was started), that family was excluded from the analyses, since data of tumour characteristics are missing in the SCR. The analyses were then based on the 1,022 pairs of brothers concordant for PCa in PCBaSe. In three families there were two concordant pairs of PCa. (Index/brother 2 and Index/brother 3).

In Paper II, the study population was selected from PCBaSe 3.0. The cohort was constructed in a similar way as in Paper I, but this time included type of brotherhood and twin status of full brothers from the STR. The brotherhood categories were – full brother. paternal half-brother, maternal half-brother, dizygotic twin and monozygotic twin. A total number of 4,262 pairs of brothers were identified.

In Paper III, data from PCBaSe 3.0 was used. After exclusion of cases with no registered histopathology data, we identified 10,441 men, <70 years at diagnosis, with low and intermediate Gleason grade group (1-2) between 2003-2012 for which we had complete follow up data. All subjects had a prostatectomy. For the main analysis, 6,638 men with preoperative Gleason grade group 1 were selected. 1,696 (26%) had FDRs with history of prostate cancer.

Figure 3.3. Flow-chart of inclusion. Paper III (unpublished)
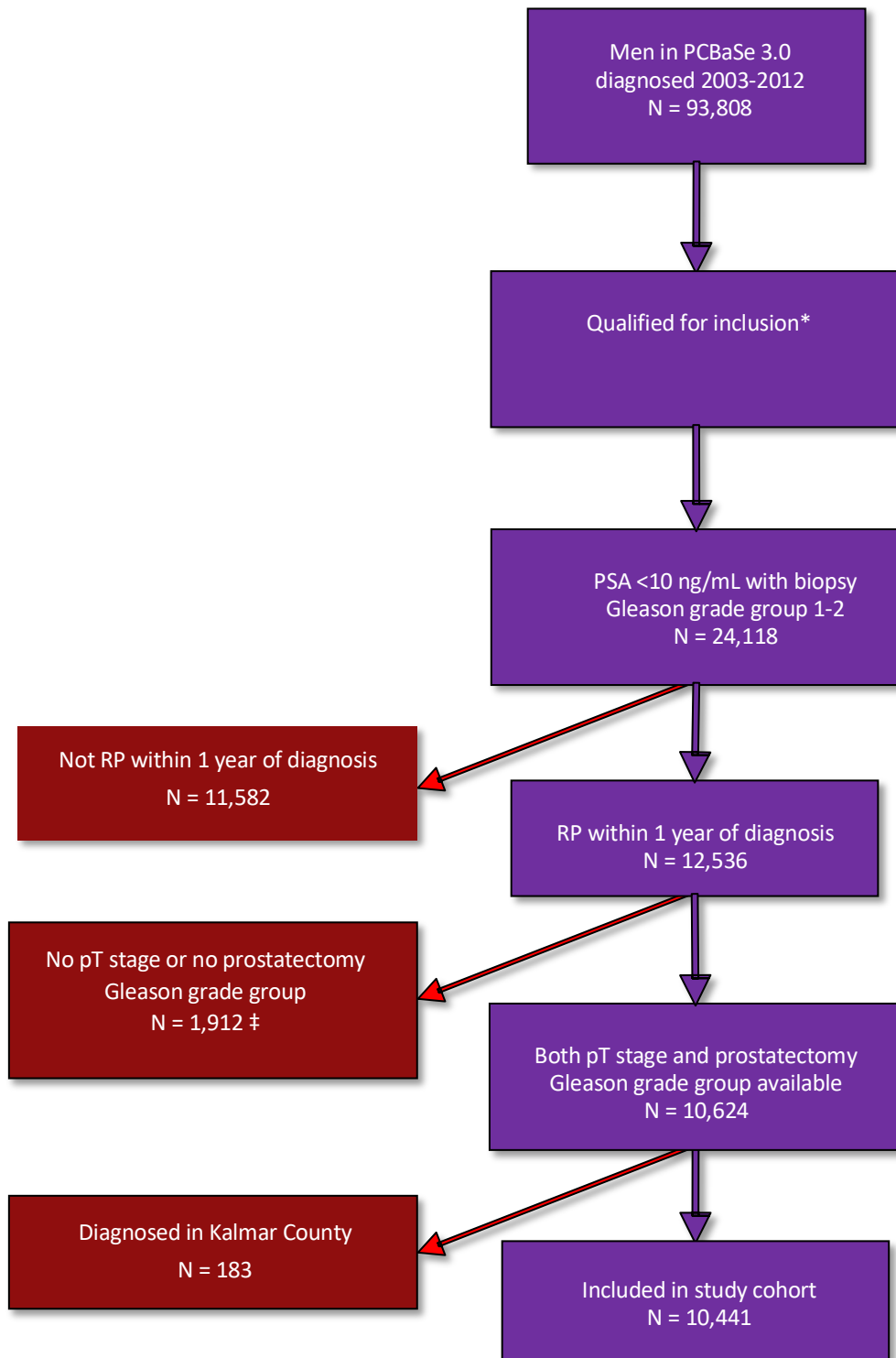
* Inclusion criteria: age ≤70 years at diagnosis, PSA <20 ng/mL, clinical stage T1-T2, not N1 or M1.
† N = 8,622 (58%) were excluded due to PSA ≥10 ng/mL and N = 6,301 (42%) had PSA <10 ng/mL but were excluded due to Gleason grade group 3-5.
‡ N = 1,861 (97%) were excluded due to missing pT stage and N = 51 (3%) had pT stage but were excluded due to missing prostatectomy Gleason grade group.

In Paper IV, the study population was selected from the Stockholm-3 study, which was a screening trial directed to men 50-69 years old in the Stockholm county, Sweden. The cohort was recruited between May 2012 and December 2014. Participants with a PSA ≥ 1 were offered a genetic test with 232 SNPs related to prostate cancer. HOXB13 was one of the analysed SNPs. Information on prostate cancer among first-degree relatives were also collected. Patients with PSA ≥ 3 were offered biopsies. For HOXB13-positive men, biopsies were offered for 1 ≤ PSA < 3[72].

Figure 3.4. Flow-chart of inclusion, Paper IV

STHLM3
(n = 58 987)

with genetic score and 1≤ PSA <100
(n = 27 578)

with biopsies taken and 3≤ PSA <100
(n = 5 536)
• with PCa (n = 2 182)
• without PCa (n = 3 354)

carriers of HOXB13
(n = 107)
• with PCa (n = 83)
• without PCa (n = 24)
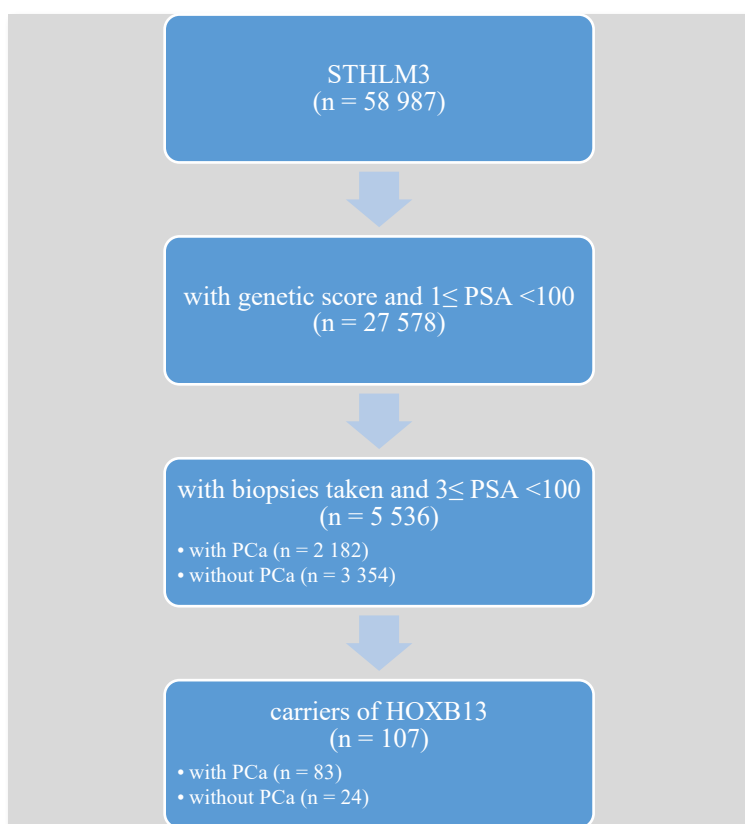
3.4 STATISTICAL METHODS

A full description of biostatistical methods is far beyond the scope of this thesis. A brief explanation of the statistical methods used in Papers I-IV is provided below.

3.4.1 Standardized Incidence Ratio – SIR

Typically used in cancer research to adjust for differences in age between subpopulations. The SIR is calculated by dividing the incidence of observed number of cases with the incidence of

expected number of cases[90]. The expected number of cases are calculated from a large population, typically a region, a state or a country. Since our study population in Study I was population-based on virtually all PCa cases in Sweden 1996-2006, the expected number of cases could be calculated internally within the study population. The interpretation of SIR is that it estimates relative risk for incidence. SIR is used in Paper I.

3.4.2 Odds and Odds Ratio (OR)

An odds is defined as the probability of an event, divided by 1 minus the probability.

$$Odds = \frac{p}{1-p}$$

Given the formula, a 50 percent probability of an event yields odds = 1. For probabilities greater than 50 percent, the odds are > 1. For probabilities less than 50 percent, the odds are < 1, but cannot be negative.

Odds ratio (OR) is the odds for an event divided by the odds for another event (= a ratio). OR can in many situations be equated with relative risk (or chance) for one event to occur compared to another event.

3.4.3 Poisson regression

The Poisson regression is a general linear model. The model can be used when the dependent variable is a count or rate. In Paper I, Poisson regression modelling is used for the time dependant differences in SIR, which is an incidence rate. The Poisson regression is popular in survival analyses where events, for example, are triggered by diagnoses of a disease, birth, deaths or end of follow-up. Poisson regression is used in Paper I.

3.4.4 Logistic regression

The logistic regression is a general linear model. In epidemiological studies logistic regression is used to estimate the influence of independent predictors (exposures) on a dependant dichotomous variable (outcome). The independent predictors are either numerical or nominal. In univariable analyses only one independent predictor is present, whereas if several predictors are added the analyses are multivariable.

General form of a logistic regression:

$$logit(p) = b_0 + b_1X_1 + b_2X_2 + \dots b_kX_k$$

The results of a logistic regression are logged odds and

$$logit(p) = \ln(Odds)$$

In studies, the interest is in how much an independent variable changes the odds. The result is presented as OR, which is the association of odds when the independent predictor is present,

compared to when it is absent. For example, an OR of 1.8 gives an 80 percent higher chance for the outcome if the exposure is present. Logistic regression is used in Paper II, III and IV.

3.4.5 Polychoric correlation and heritability

Polychoric correlation are usually calculated from data in a contingency table. Tetrachoric correlation is a special case for data in a 2x2 contingency table. The levels in the contingency table must be ordered and the underlying trait must be continuous and normally distributed.

Example: The severity of disease is normally distributed in the population. It may be convenient to categorize the severity to decide a threshold for intervention. The levels are set to mild or severe.
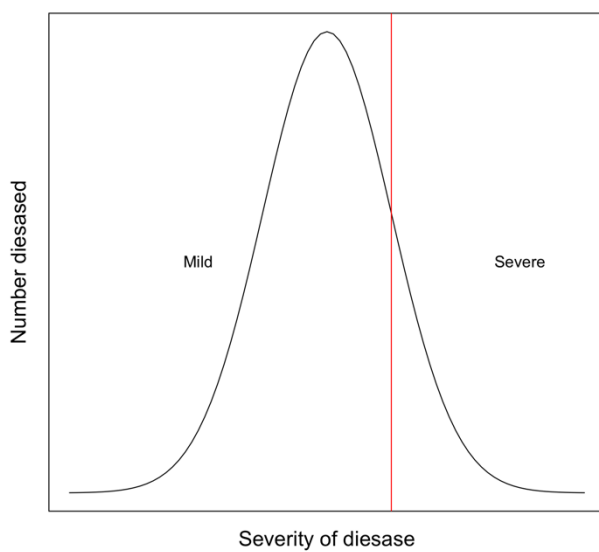
If two population with the same disease and mutual exposure are put into a contingency table, the degree of correlation can be estimated using polychoric correlations.

Population 1 / Population 2	Mild	Severe
Mild	*a*	*b*
Severe	*c*	*d*

If the numbers in *a* and *d* are high, and low in *b* and *c*, the correlation is high and vice versa. From the example, it is obvious that the correlation is highly dependent on where the threshold is put.

The polychoric correlations can be used to calculate heritability[31] which is a descriptive method often used in twin studies. The definition of heritability is the proportion of variance in phenotype that explains the variance in genotype. The underlying assumption as that monozygotic twins share 100% of the genome and dizygotic (and non-twin siblings) share 50% of the genome.

Heritability as calculate in Paper II:

$$heritability_{(0-1)} = \frac{polychoric\ correlation}{k}$$

Where k=1 for monozygotic twins and k=0.5 for dizygotic twins and full siblings.

In Paper II, the underlying trait is PCa and the levels are set to low risk and non-low risk. The populations compared are pairs of brothers where the first diagnosed brother belong to population 1 and the second brother to population 2. Estimates on heritability is used in Paper II.

3.4.6 Imputation

Missing data is common within all fields of science. For each patient (row) in the dataset there may be one or several variables missing. If the variables are essential (i.e. describe an outcome, exposure or independent predictor) that patient must be excluded since it is impossible to interpret the patient's contribution to the end result of a statistical analysis. Excluding all patients with missing data is called a complete-case analysis. Under the condition that the missingness of data is relatively small and missing at random, it may be acceptable to perform a complete-case analysis without jeopardising statistical robustness[91]. Systematically missing data is a form of differential misclassification that leads to selection bias. Imputation is about how to replace the missing data with reasonable estimates drawn from the distributions of the variables with missing values[92].

A literature search in PubMed reveals that imputation is becoming more common within science, especially during the last decade. The drawback of using imputation is that you may introduce unreasonable values in the dataset leading to results drifting in a more positive (or negative) direction. The upside is that information from incomplete cases are not ignored, making the analysis more powered as they are based on more data and can compensate for the biased result that may come with complete-case analysis.

Multiple Imputation by Chained Equations (MICE) is used in Paper II. Each independent variable with missing data is regressed as if it was the dependant variable and then replaced with the predicted estimates. A cycle denotes when all variables have been replaced with predicted values. The cycle is then repeated multiple times to refine the results. How many cycles are needed is dependent on the level of missingness in the dataset[91,93]. Imputation is used in Paper II.

3.5 STATISTICAL ANALYSIS

3.5.1 Paper I

To estimate the relative risk of Gleason score-specific prostate cancer between brothers we used standardized incidence ratio (SIR) stratified by Gleason score of the index case. Gleason score was divided into three categories (2-6, 7, 8-10) representing low, intermediate and high-risk disease. The categorization was applied on both index men and their brothers. Overall SIR was calculated for the study period. Further, we introduced a time scale by splitting the study period into 1-year period-specific rates. Using Poisson regression models, changes in SIR over time could be estimated.

3.5.2 Paper II

Today, the line between low and intermediate risk tumours demarks the line for which active surveillance or curative/palliative treatment is recommended. All men were therefor divided into low or non-low risk groups, where the non-low group consists of the intermediate and high-risk group. Pairs of brothers were stratified into full brothers, half-brothers (maternal and fraternal separately) and mono-/dizygotic twins. We then used standard logistic regression models with a dichotomized outcome to estimate odds ratios that brothers were concordant in risk group. Polychoric correlations were used to assess heritability. For missing values, we used multiple imputation by chained equation (MICE).

3.5.3 Paper III

ISUP-grade (in Paper III denoted Gleason Grade Group - GGG) and stage at diagnosis was compared with the postoperative grade and stage. The analysis was separated for subjects with preoperative ISUP-grade 1 and 2. Men were stratified into exposure groups. Men without any first-degree relatives (FDR) with PCa, men with any FDR with PCa, any FDR dying from PCa <80 yr. or a brother with high-risk or metastatic PCa. Standard logistic regressions, uni- and multivariable complete-case analyses, were applied to estimate odds ratio. The multivariable analyses were adjusted for factors significant in univariable analyses. In Paper III, only the analyses on ISUP-grade 1 was reported.

3.5.4 Paper IV

Descriptive analyses were applied to calculate prevalence of HOXB13 G84E mutation carriers. Significant cancer was defined as ISUP ≥2. The term significant cancer reflects patients with prostate cancer who should be considered for treatment. Significant cancer may be a better term than non-low risk prostate cancer, used in Paper II. The genetic score as calculated in the original study[72] was included in the data set. The genetic score is a summary estimate for all included SNPs. The number of risk alleles are multiplied by the logarithm of the odds ratio for each SNP. High genetic score reflects stronger exposure to SNPs associated with PCa. Standard

logistic regression, uni- and multivariable, estimated risk for significant cancer among carriers of HOXB13. Only co-variables significant in univariable analysis were used in the multivariable analyses. In multivariable analyses only genetic score without HOXB13 was included as co-variable since HOXB13-status was a separate variable.

4 RESULTS

4.1 PAPER I

1,022 pairs of brothers with concordant PCa were identified. The overall SIR for the second brother to be diagnosed with prostate cancer was 3.1 (95% CI, 2.9–3.3). Detection diagnoses at health check-up was more common among brothers than among index cases. (44.1% vs 31.9%). The proportion of metastatic disease was lower, and the proportion of low-risk cancers was higher among the brothers compared with the index cases. In Figure 4.1, SIR is presented for prostate cancer with low, intermediate and high-risk Gleason score, stratified by the Gleason score of the index cases. SIR for Gleason score ≤6 was 3.48 (95% CI, 3.13–3.86) and 2.07 (95% CI, 1.55–2.70) for Gleason score ≥8 if the index case had Gleason score ≤6. Conversely, SIR for Gleason score ≤6 was 2.53 (95% CI, 1.97–3.21) and 4.00 (95% CI, 2.63–5.82) if the index case had Gleason score ≥8.

Figure 4.1. Overall SIR for concordance in Gleason score (unpublished)
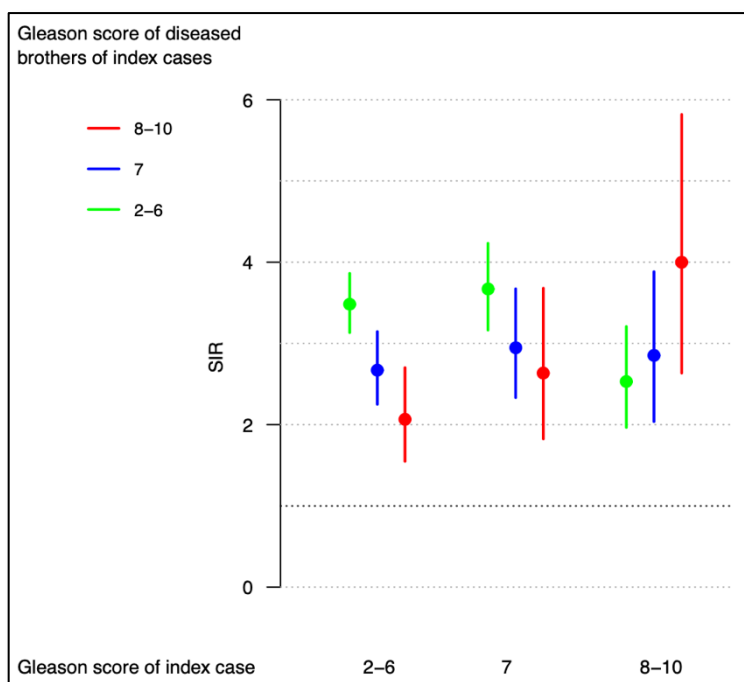
In a sensitivity analysis, the SIR for each Gleason score category was estimated when excluding diagnoses within the first year after the index brother's diagnosis, tumours detected through health check-ups (opportunistic screening) and diagnoses among half-brothers. Only minor changes were observed and the pattern of Gleason score concordance remained.

Figure 4.2. Overall SIR for concordance in Gleason score, with exceptions (unpublished)
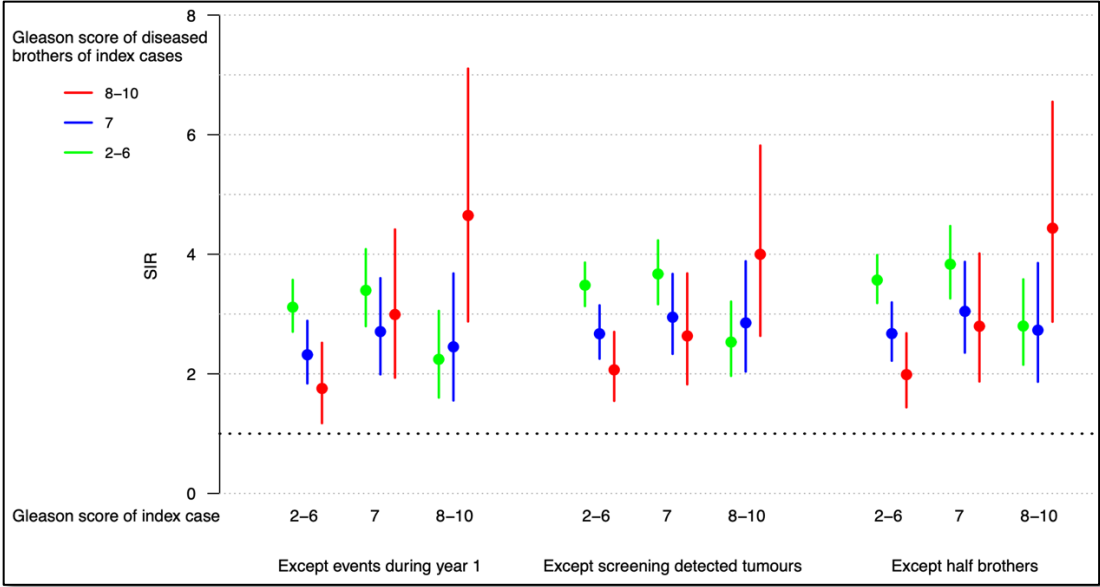
With time since the diagnosis of the index case, the SIR generally decreased among brothers (Figure 4.3). The exception was brothers to index cases diagnosed with intermediate or high-risk tumours. For them, the SIR for Gleason score ≥8 tumours increased with time.

Figure 4.3. Estimated changes in SIR during follow up
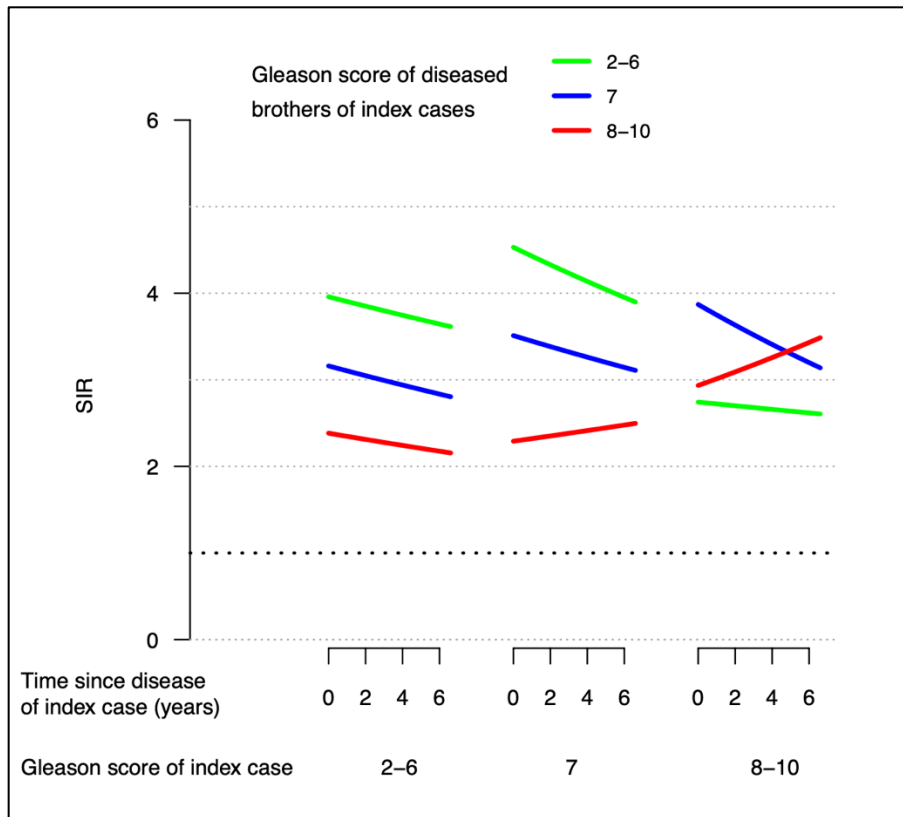
Jansson, Eur Urol 2012

4.2 PAPER II

With six years more of follow-up compared to Paper I, the cohort of PCa concordant brothers was now 4,262. With linkage to the Twin register, information on zygosity was obtained. Table 4.1 presents number of brother pairs for who risk category could be assigned.

Table 4.1. Low-Risk Versus Non–Low-Risk Prostate Cancers Among Brothers Concordant for Prostate Cancer

| | | Index Brother With Low-Risk Cancer | | | | Index Brother With Non–Low-Risk Cancer | | | |
| | | Second Brother With Low-Risk Cancer | | Second Brother With Non–Low-Risk Cancer | | Second Brother With Low-Risk Cancer | | Second Brother With Non–Low-Risk Cancer | |
Brother Type	Total No. of Brother Pairs	No. of Pairs	%*	No. of Pairs	%	No. of Pairs	%	No. of Pairs	%
Monozygotic twin	57	10	67	5	33	15	36	27	64
Dizygotic twin	34	11	55	9	45	6	43	8	57
Full brother	3,556	545	43	708	57	884	38	1,419	62
Paternal half-brother	38	8	53	7	47	7	30	16	70
Maternal half-brother	45	5	45	6	55	14	41	20	59

*Percentage by row and by index risk category.

Jansson, J Clin Oncology 2018

The adjusted OR for sharing non–low-risk status for full brothers was 1.21 (95% CI, 1.05 to 1.40). Among monozygotic twins, the OR was 3.82 (95% CI, 0.99 to 16.72).

Figure 4.4. Odds ratios. Low vs Non-low risk PCa
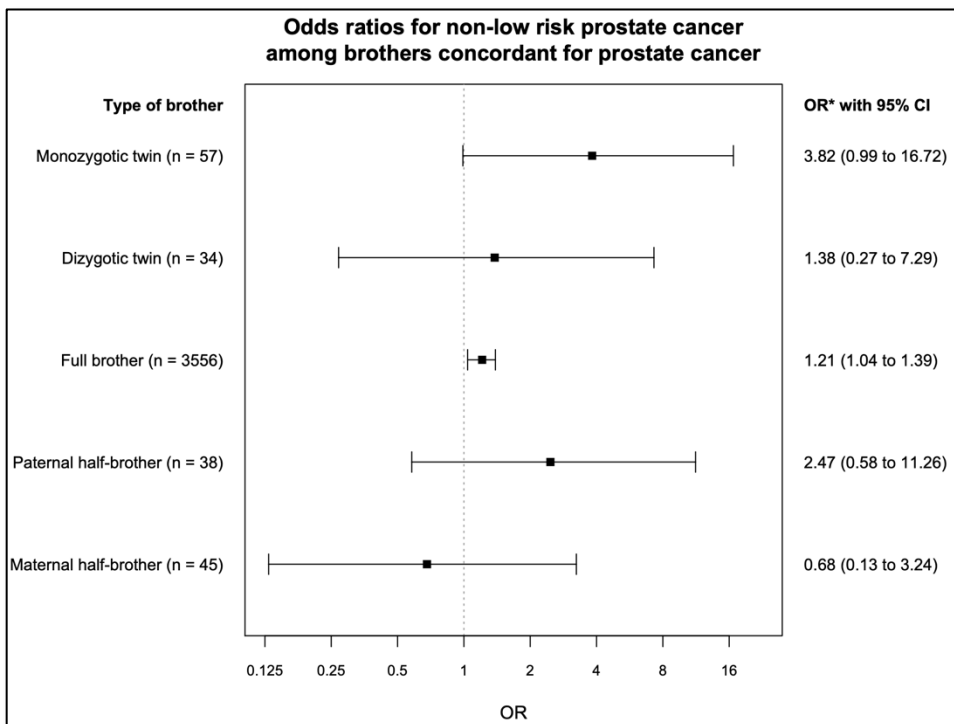
Jansson, J Clin Oncology 2018

Similar results were obtained by restraining the analyses to diagnoses occurring within 4 years. The within-pair median time between the diagnoses was significantly shorter (2.8-4.1 years) for monozygotic twins compared to other types of brothers. Further, imputation did not change the results.

The estimates of heritability were 45% (~ 95% CI, 7-82%) for monozygotic twins and 16% (~95% CI, 6-26%) for full brothers. For all other brother types, the results were insignificant.

4.3 PAPER III

Of the 6,638 men with preoperative ISUP 1, 74% had clinical stage T1. 26% had an FDR with PCa. No difference in the probabilities of upgrading and upstaging was found comparing men with and without a family history of prostate cancer.

In univariable analyses, several tumour characteristics were significant for postoperative adverse pathology.

Table 4.2. Logistic regression models with odds ratios (OR) for upstaging and upgrading in men with biopsy Gleason grade group 1.

	Upstage		Upgrade	
	Crude OR	**95% CI**	**Crude OR**	**95% CI**
Age at diagnosis				
<60 years	1.00	(Ref.)	1.00	(Ref.)
60-64 years	1.05	(0.90-1.24)	1.15	(1.02-1.30)
65-70 years	1.59	(1.37-1.86)	1.49	(1.32-1.69)
Clinical T stage				
T1	1.00	(Ref.)	1.00	(Ref.)
T2	1.56	(1.35-1.79)	1.29	(1.15-1.44)
Serum PSA				
<4 ng/mL	1.00	(Ref.)	1.00	(Ref.)
4-5.9 ng/mL	1.41	(1.15-1.71)	1.18	(1.02-1.36)
6-9.9 ng/mL	1.82	(1.50-2.21)	1.32	(1.15-1.52)
Proportion of positive cores				
<25 %	1.00	(Ref.)	1.00	(Ref.)
25-49 %	1.46	(1.25-1.71)	1.18	(1.05-1.33)
50-100 %	2.20	(1.87-2.60)	1.34	(1.18-1.53)

Univariable. Complete-case analysis (excluding men with missing data), n= 6,638

For all cases diagnosed 2009-2012 the dataset had a separate variable for PSA density, which was significant for both upstaging and upgrading.

Table 4.3. Logistic regression models with odds ratios (OR) for upstaging and upgrading in men with biopsy Gleason grade group 1.

Family history[a]	Upstage[b]		Upgrade[b]	
	OR[d]	95% CI	OR[d]	95% CI
Group 0	1.00	(Ref.)	1.00	(Ref.)
Group 1[c]	1.00	(0.86-1.16)	1.00	(0.89-1.12)
Group 2[c]	1.06	(0.76-1.47)	1.17	(0.91-1.50)
Group 3[c]	0.93	(0.58-1.48)	1.33	(0.94-1.87)

[a]Family history:

- Group 0 = No familial prostate cancer,
- Group 1 = Any first degree relative with prostate cancer,
- Group 2 = First degree relative dying of prostate cancer before the age of 80 or brother with high risk prostate cancer or brother with distant metastases,
- Group 3 = Brother with high risk prostate cancer or distant metastases at diagnosis

[b] Adjusted for age, clinical T stage, serum-PSA and proportion of positive cores

[c] Family history groups are not mutually exclusive, and each is compared to the reference group (group 0)

[d] Multivariable. Complete-case analysis (excluding men with missing data), n= 6,638

Similar results were found for men with preoperative ISUP 2.

As the estimates were borderline significant, we did a post hoc power analysis. For upstaging, there was 80% power to detect 40% increase. For upgrading we had more than 90% power to detect 30% increase. The power analysis was based on exposure group 2.

4.4 PAPER IV

In this population-based cohort of men aged 50-69 with PSA between 1 and 100, the prevalence of HOXB13 G84E was 1.3% (359/27,578). In the subgroup of 5,536 men with biopsy data from pathological reports, the prevalence was 1.9% (107/5,536).

In univariable analysis, risk of any PCa among HOXB13 G84E carriers was OR 5.47 (CI 3.52-8.83). For clinically significant cancer the OR was 2.84 (95% CI, 1.90-4.20). The risk persists in multivariable analysis with OR 2.10 (95% CI, 1.34-3.26) (Table 4.4).

Table 4.4. Risk of PCa, multivariable analysis among men with biopsy data and ≥ 3 PSA <100

Risk of PCa. Multivariable analysis	Any PCa		Significant PCa*	
	OR	CI95	OR	CI95
scoreNoHOXB13	1,50	(1.39-1.62)	1,25	(1.13-1.38)
her	1,59	(1.34-1.87)	1,34	(1.09-1.64)
HOXB13	**4,67**	**(2.93-7.73)**	**2,10**	**(1.34-3.26)**
TotalPSA	1,11	(1.09-1.14)	1,18	(1.15-1.21)
AgeDiag	1,03	(1.02-1.05)	1,05	(1.04-1.07)
ProstateVolume	0,98	(0.97-0.98)	0,96	(0.96-0.97)

* = Significant PCa defined as ISUP≥2
(OR reflects benign+ISUP1 vs ISUP≥2)

PCa among FDRs (variable 'her') increases the risk of any PCa by OR 1.59 (95% CI, 1.34-1.87) and for significant cancer 1.34 (95% CI, 1.09-1.64) in multivariable analysis. Prostate volume had no clinically significant meaning for prostate cancer risk.

Among non-carriers of HOXB13 G84E, 13.8 percent stated that they have at least one first-degree relative with prostate cancer. The corresponding percentage for carriers of HOXB13 G84E was 18.7%.

The absolute risk for a HOXB13 G84E-positive man with PSA >1, to be diagnosed with any PCa was 37%. Absolute risk for significant PCa was 14%.

Table 4.5. Absolute risk of PCa

	HOXB13 neg		HOXB13 pos	
no PCa	24 591	90,4%	225	62,7%
any PCa	2 601	9,6%	**134**	**37,3%**
Low grade PCa	*1445*	*5,3%*	**83**	**23,1%**
Significant PCa	*1156*	*4,3%*	**51**	**14,2%**

In the subgroup with biopsy data, the HOXB13 G84E carriers were significantly younger with median age 61.4 years compared to 64.7 years for non-carriers.

Genetic score predicts higher risk of any PCa but does not differentiate low ISUP grade from higher ISUP grades, regardless of family history. In univariable analysis the OR for genetic score is similar with, 1.65 (95% CI, 1.54-1.78), and without, 1.58 (95% CI, 1.47-1.70) the influence of HOXB13 G84E. Interestingly, men with high genetic score (+2SD), have reported FDRs with PCa is two-folded compared to men with low genetic score (-2SD).

Figure 4.5. Reported PCa among any FDR related to genetic score
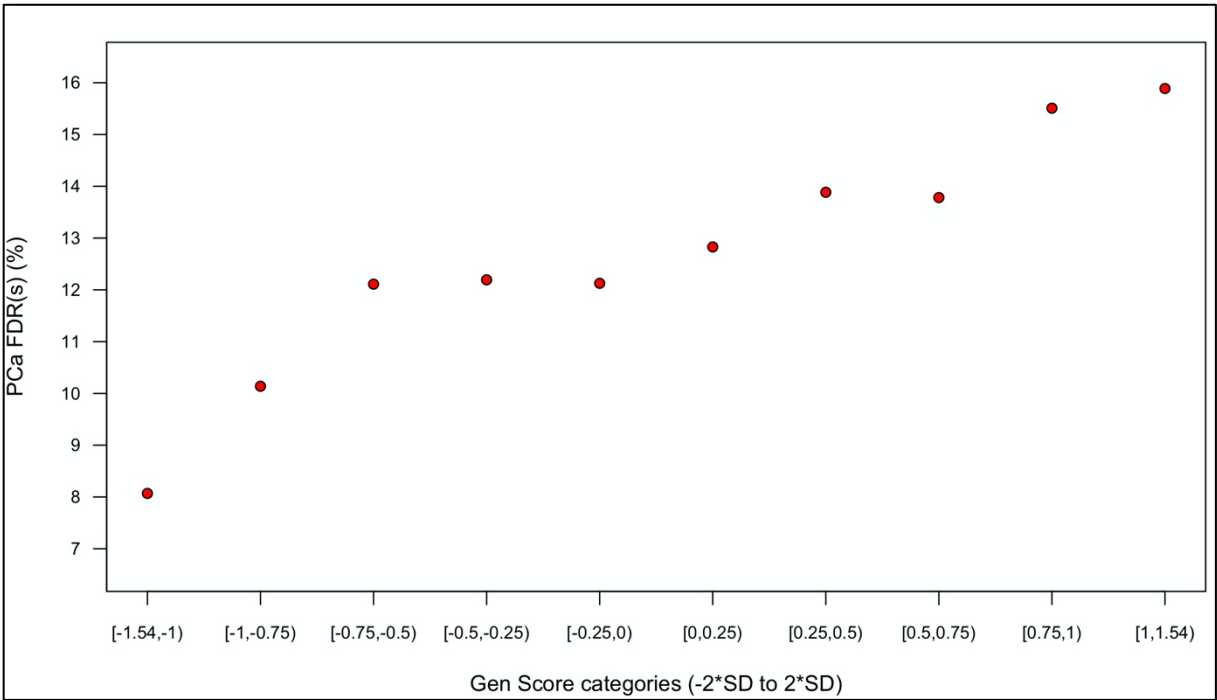
Prevalence of HOXB13 G84E increases with higher PSA levels, from 1% for PSA ~1 to 4.5% for PSA >20 (Figure 4.6). Median PSA for non-carriers of HOXB13 G84E was significantly lower (PSA$_{median}$=1.9 ng/ml) compared to carriers of HOXB13 G84E (PSA$_{median}$=2.3 ng/ml)

Figure 4.6. Prevalence of HOXB13 G84E and PSA-level
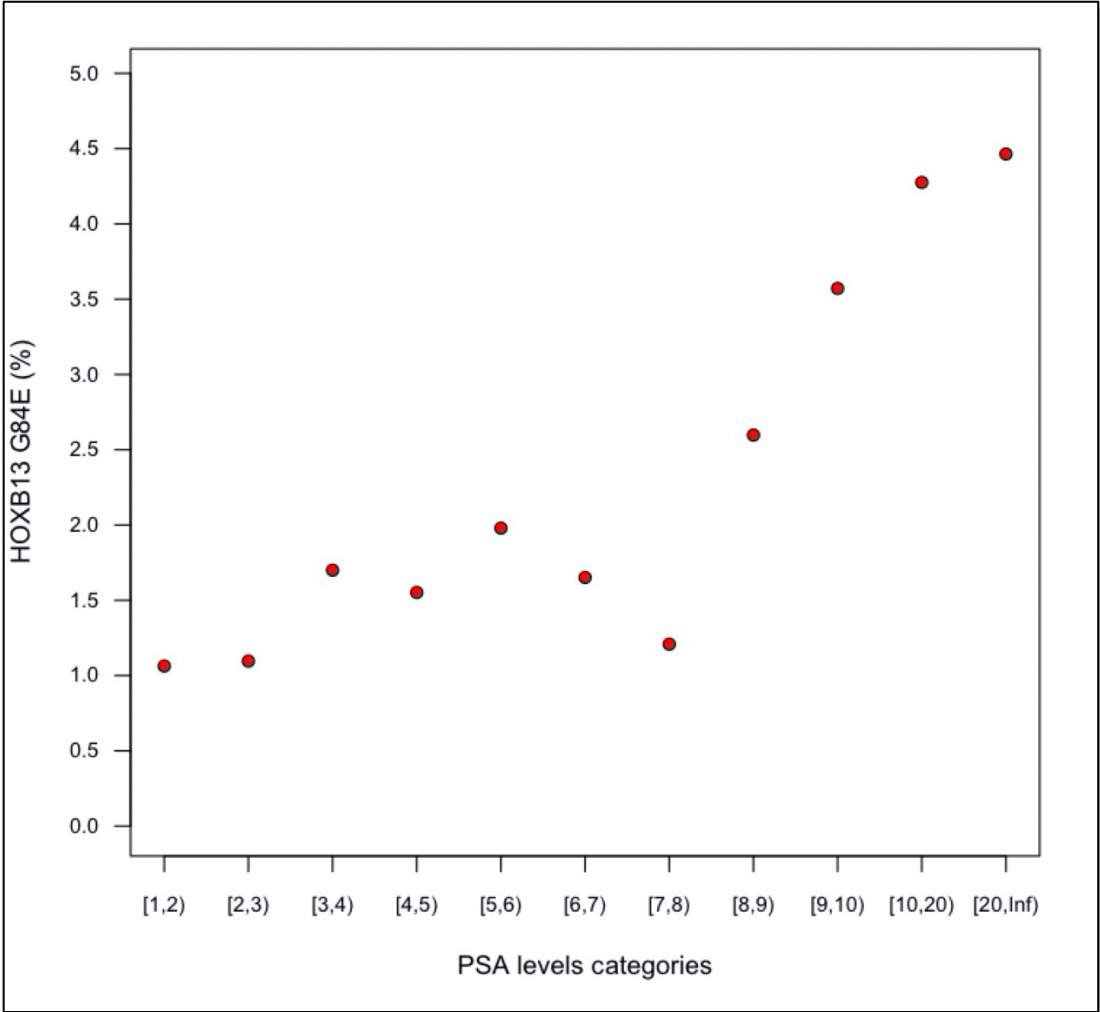
5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

Early studies on familial prostate cancer are mostly based on patient-reported positive family history[42]. Finding pairs of brothers via linkage in national registers does not rely on surveys among family members and thus reduces the information bias. The development of large national registers in Sweden, and other Nordic countries, are based on PINs provided to each citizen. The PIN is used as a linkage key to extract data from several registers and thereby provides an option to build large flexible databases with more valuable information compared to standard cancer registers.

Depending on study design, register based studies have many advantages. Collecting data for a randomized trial or case-control study can be very time consuming. Registers collecting data prospectively over time may reduce recall bias as patients does not need to remember details of potential exposures or previous diseases. As the potential hypothesis have not yet been formulated it also reduces selection bias if the register has high inclusion rate. The registers are usually large and population-based over a region or country which enables splitting the cohort into subpopulations maintaining statistical power. Depending on the hypothesis for a study, the register can easily provide a control group, matched for age, mode of treatment etc. Registers are also well suited for studies of diseases with slow progression, which may not be practically feasible or cost-effective in randomized trails[94].

There are also limitations. Registers are never better than the data registered. As the data is registered by many different administrators or institutions, there may be missing and misclassified data in the register. There may also be a tendency to register diagnosis or treatments with higher economic compensation. As registers more and more are being used for comparisons between health care providers, there may be information bias if registration of treatment failures and complications is systematically omitted. Selection bias from systematic errors drives the result towards larger or smaller differences, between groups of patients, that may not exist. Random misclassification errors dilute the differences and important findings may not be observed.

Thus, researchers have limited abilities to check the validity of the data as they are provided with deidentified data. Studies on different treatments are prone to selection bias because allocation of patients to different treatments have not been randomized. Randomized trails are the gold standard for head-to-head comparisons of treatment modalities.

The researcher must rely on the existing variables. If new predictors are discovered the process of adding new variables to a register is time consuming and it takes long before the new data in question can be used.

Outcome measures in Paper I-IV are all dependant of stratifying men with PCa into risk groups. Different approaches are used. In Paper I only total Gleason score is taken into account in the

assessment. In Paper II, the common tumour characteristics (Gleason score, Stage and PSA) are used to create risk group strata. We use the term non-low risk which denotes all patients that cannot be classified as low risk. This was done as the power would be too low if the analyses were based on several risk groups. In Paper III, we use Gleason Grade Groups (equivalent to ISUP grade) for assessing upgrading in postoperative prostatectomy specimen. The grade groups provide higher resolution in the intermediate risk group according to D'Amico[15] as Gleason score 7 is separated into intermediate low, 3+4 (GGG/ISUP 2) and intermediate high. 4+3 (GGG/ISUP 3). Pathological upstage is a separate outcome. Then in Paper IV we instead used the term significant cancer, which is similar to non-low, but based on Gleason (ISUP) grade only.

Comparing prognosis of different risk groups between studies is challenging, and we did not succeed to use the same definition in all studies within this thesis. What brings the dichotomized outcome measures together in Paper II and IV though, is the modulation of increase in relative risk for prostate cancer, where active treatment should be recommended for the patients according to contemporary guidelines.

Re-evaluation of the histopathology in Paper I-III would have reduced random misclassification and address the stage migration[12] that has occurred for prostate cancer pathology during the study period. On the other hand, there is no reason to suspect that these random errors would be more present in the registered data for one of the brothers within each pair. In Paper IV, this potential bias is reduced, since all pathology was evaluated by the same pathologist.

5.2   CLINICAL IMPLICATION

In Paper 1, we found among 1,022 pairs of brothers with PCa that there is a concordance in Gleason grade at diagnosis. The risk of the second brother to be diagnosed was increased within the first year, since diagnosis in PCa for a man probably triggers his brother(s) to test themselves. Accordingly, risk of diagnosis decreased over time. For index brothers with high risk Gleason grade disease (Gleason score 8-10) the risk of his brothers increased over time. We concluded that the natural history of PCa will demask itself over time for high grade tumours, in contrast to indolent tumours that are found due to behavioural reasons.

An advantage of studying pairs of brothers is that difference in ages is small (half-brothers excluded). The median age difference between full brothers with concordant PCa in Paper II was 4.7 years. (Median time between diagnoses was 4.1 years). Both brothers will then be treated in about the same era of knowledge when it comes to diagnostic work-up and treatment. It can be argued that in 5 years, diagnostics and treatment have time to change significantly. However, diagnoses with prostate biopsies and curative treatment options with radiation or surgery have not changed during the study period of this thesis.

With knowledge of the concordance in Gleason score among pairs of brothers from Paper I we sought to investigate if this also could be reflected in different types of brothers where monozygotic twins present highest rate of genetic similarities. This restrained the analysis even harder. Not only did we have to find pairs of brothers with PCa, they also had to be twins. With the relatively small number of twin pairs, we found a gradient of increasing risk for non-low risk PCa by dose of shared genes, but with insignificant estimates.

If prognosis in PCa is partly explained by a mix of multiple genetic factors, it is logical to believe there would be similarities in how the disease is presenting within biological families and have a similar natural course. The natural course can only be fully observed if no intervention is done. Today, in modern countries with high level of healthcare, that is rarely seen in any cancer form. Studies of cancer diseases like PCa, are in a way hampered by this fact. We need methodological techniques and good prognostic markers to come around this. Genetic markers are likely to come on broad front and maybe revolutionize medical decisions and estimation of health risks. Yet, basic information about family history adds an extra dimension to genetics since even though somebody has a mutated gene, we may still don't know if it is an oncogenic mutation or not. With affected relatives we can conclude that it probably is an oncogenic mutation and estimate the pathological penetrance. The conclusions in Paper I and II points towards that there seems to be common factors in tumour characteristics when brothers are diagnosed with PCa.

A challenge with risks estimated on large population is to translate these risks to the individual patient. How patients handle risk differs significantly. Depending on their personality and for example, level of anxiety or general risk-taking behaviour, patients reason differently[95]. What seems to be a high risk for one patient may be regarded as low risk for other patients.

In Paper III, the risk we calculate is if there is extra risk added for postoperative upstaging or upgrading for a man with FDRs with high risk PCa. We did not find any addition risk for upstaging or upgrading. For the individual patient it may though be reasonable to think there is a risk for worse PCa solely because there is aggressive or mortal disease in the family and thereby overlooks stronger predictors of prognosis embedded in the tumour characteristics of his own diagnosis. As doctors, we should be aware of the differences in absolute and relative risks when counselling the patients. In this case, the risk of upstaging or upgrading is substantial about 30-40%, for any patient and not just those with family history of PCa. The widespread use of MRI and targeted fusion biopsies in recent years have potential to decrease the rates of adverse pathology.

The low prevalence of moderate to high penetrant genes makes it challenging to decide who should be tested. Including all known genetic markers in a screening program would probably have limited use on a population level but may be very expensive. As more than 100 susceptible gene mutations are known, emphasis should be on finding genes with impact on prognosis.

In Paper IV we found about nearly five-folded increase in risk for any PCa, and the risk for significant cancer doubled.

The prevalence of HOXB13 G84E appears to be related to elevated PSA-level. With higher PSA-level, HOXB13 G84E-positive men are more likely to be recommended and undergo biopsy of the prostate. The lower mean age observed among HOXB13 G84E-positive men with PCa supports this conclusion.

Inclusion criteria in the original screening study was partly based on PSA level (PSA≥1). In the analyses comparing carriers with non-carriers, that potential bias was addressed by excluding HOXB13 G84 carriers with ≥1 PSA ≤ 3. The increase in risk may still, to some extent, be attributed to detection bias. Genetic score estimates with and without HOXB13 G84E were similar and suggested that HOXB13 G84E only explains a small portion of familial incidence of PCa at population level.

In Paper IV, the study population was a population-based cohort recruited from the Stockholm county. All specimen from the biopsies were interpreted and reported by a single pathologist. Information of ethnicity was lacking. According to publicly available population data at time for recruitment[96], 74% of the male population in the Stockholm county were born in Sweden. History of PCa among any FDRs was self-reported and lacked information on the FDRs prognosis and HOXB13 G84E status. It is also possible that some of the men in the cohort were in fact FDRs (e.g. brothers).

As HOXB13 G84E may predict significant PCa, it can be argued that carriers should be advised genetic counselling. On a population level though, the impact of HOXB13 G84E on risk of PCa is low. A debate about a general program for screening/organized testing for prostate cancer is ongoing. If genetic testing is included, HOXB13 G84E would probably qualify as one of the genetic markers to test for.

The results of our studies are based on the fact that not only the family history is known, but also on tumour-specific data in first-degree relatives. In order to be used in the counselling situation, these data must therefore be known. It is not reasonable to ask the individual patient to provide the information. Retrieving the information encounters confidentiality problems as an individual doctor, probably do not have a caregiver relationship with the patient's relatives.

However, a few questions can provide a decent answer as to whether the patient's brother had severe prostate cancer or not. (Table 5.1)

Table 5.1. Example questions for assessing familial occurrence and severity of prostate cancer

Question	Interpretation of answer
How old was your brother when he was diagnosed with prostate cancer?	Early onset indicates familial aggregates of cancer
When your brother was diagnosed, was he then recommended curative treatment?	The brother's tumour was at least of intermediate risk
If so, did he receive treatment and is still free of prostate cancer?	Depending on time since treatment, but so far, his brother is either cured or the cancer has relapsed.
If not, how is the status of your brother's prostate cancer today?	The answer will indicate either aggressive cancer (locally advanced, metastatic or mortal disease) or low risk because the brother was recommended active surveillance.

5.3 ETHICAL CONSIDERATIONS

The emergence of large registries in Sweden can be viewed from a historical perspective. We have long had an acceptance for our lives and movements are recorded in different ways. A society where that it is possible needs a stable democracy where people have great confidence in state power and trust that the collected data is used for a good purpose. In countries with a different history, especially a history of dictatorship, people may have a different view of the State's role and it can be difficult to gain acceptance for the establishment of registers.

However, I believe that registers are always a restriction of privacy but there are many examples of where benefits to society still goes before, such as population registers, tax agency's various records, criminal records and records in health care. Modern society could not function without accumulated knowledge about the people living there. Herein lies the great challenges - enough information without going down at an excessive level of detail and to protect data so that only necessary information is used for the purpose intended.

Great acceptance for the establishment of registers in health care testifies to the fact that today in Sweden, more than 100 national quality registers exist[97]. For researchers it means unique

opportunities. Most people primarily look at these records as part of health care that can help improve the health of themselves or their relatives and secondly, a source for research. There would probably be less acceptance if the registers were primarily for research purposes.

It's important to ensure that people understand that participation in a national quality register is voluntary and does not mean that they would receive worse care if they decline to participate. On the other hand, mass defections from the national quality registers would violate the scientific validity and potentially constitute an ethical problem by the selection bias that arises. Important questions concerning follow-up of diseases or who should be treated may not be answered or wrong conclusions be drawn.

We assume in most cases that patients or their guardians are competent in making decisions. But even if they are, how can we be sure that they understand all aspects of participation in a register? Can we as scientists and doctors understand it? Can we, in the individual case, lean on the assumption that in Sweden there is a general acceptance of national quality registers?

It is hard to see any direct disadvantages for the patient. By allowing national quality registers a special position in the Patient Data Act (Patientdatalagen) society undertakes a responsibility to handle errors. Each quality register is also subject to the EU's General Data Protection Regulation (GDPR). The information in the registers must be protected to prevent outsiders from accessing the information. Equally important is that information should never be disclosed without interpretation. For a scientific article or a report from the medical care principals, the risk is low. But if raw data are presented in media, there is a clear risk of misinterpretation. Thus, it's a balancing act of not keeping information secret and preventing it from doing harm if it is interpreted wrongly. For example, if the perception of prognosis for a particular disease is distorted, it may involve difficulties in matters relating to insurance, employment, opportunities for adoption, or other situations where health is included in the assessment.

In this thesis, where diagnosis, treatment and prognosis have already been taken into account there are still pitfalls. When large amount of data is processed, there may be situations where the data is stratified and divided into small groups. Potentially, it becomes possible to identify an individual patient or group of patients. You are then close to the limit that can be considered acceptable and perhaps not in the context of the ethical state. For example, I have in my studies a split in several groups where the smallest consists of a few dozen pairs of brothers. If we hypothetically introduce a geographical parameter in the studies, it is easy to realize that the risk of identification increases markedly.

Finally, collecting large amounts of information for long periods may contribute to a jaded attitude. People have so much to deal with in everyday life and the standpoint taken in some issues can easily become a routine not given much thought. So, is a silent indifferent acceptance worth as much as a regular active stance? Obviously not, but in practice it has to be accepted to a certain degree.

6 CONCLUSIONS

There is a concordance in histopathological tumour characteristics among brothers with PCa

There seems to be an association between average proportion of shared genes and concordance for risk group among different type of brothers

Family history does not seem to add extra risk of postoperative upstaging or upgrading after prostatectomy for low risk PCa. Men with low risk PCa should not be advised differently to men without family history of PCa in terms of risk for postoperative upstaging or upgrading.

The rare HOXB13 G84E mutation is associated with elevated PSA-levels increase risk for any PCa markedly, and significant PCa moderately in a population-based screening cohort in the Stockholm county.

7 FUTURE PERSPECTIVES

7.1 FAMILY HISTORY AND IMPACT ON MORTALITY.

The original idea for Paper II had a similar hypothesis as Paper I. Instead of concordance in Gleason grade, we would analyse concordance in PCa-specific mortality. That data, however, was not mature enough for relevant conclusions. The reason is that linking of men into families requires the MGR. As described above, the oldest person we can find is born 1932. From that fact follows that the oldest person in the cohort in Paper I was about 75 years old. Many patients diagnosed and dying from prostate cancer are considerably older. There were simply too few events within the registers were the second brother diagnosed has died of prostate cancer. In PCBaSe 4.0 with another 10 years of follow-up and twice as many patients, it would be possible to conduct a study that combines Paper I and II and add prostate cancer-specific mortality as outcome in survival analysis.

7.2 INCLUDE FAMILY HISTORY IN PREDICTIVE MODELS

At present, in major guidelines, family history is part of the decision-making when recommending men to undergo clinical examination and PSA testing for PCa. If we have solid data to predict the added value of family history in prostate cancer-specific mortality, family history could be validated and potentially added to the general accepted risk assessment models like the D'Amico risk stratification groups, the MSKCC nomogram or the CAPRA score. However, it would require more detailed information when documenting patients' medical history as suggested above. The information should then be added to the medical records in a structured way to simplify automatic inclusion in the risk assessment and registers.

7.3 BUILDING LARGER DATABASES

The use of national registers within the Nordic countries based on personal identifications numbers opens up for co-operation of health registers. The Nordcan database links the National cancer registers of all Nordic countries[1]. The build-up of cancer-specific clinical registries have not reached that far in terms of international collaboration projects. Current available PCa registries are found in high-developed countries in Europe and North America[98]. The PIONEER project is an EU-funded database project linking patient- and research data from public and private sources[99]. A big data project like PIONEER aims to find risk factors, prognostic predictors and patient related characteristics such as gene profiles to improve prostate cancer treatment. In general, we probably underestimate competing risks in prostate cancer. Combining data from stroke, heart and diabetes registers with cancer registers should

provide better predictors to decide who will benefit from treatment. Big data have the potential to increase external validity and exponentiate the power in all studies presented in this thesis. The price for big data may be at the expense of less quality. Extensive work has to be done to maintain validity of data sources which includes updating and removing obsolete data.

One might ask if there is an end stage for large registers? May we have global registries one day?

8 ACKNOWLEDGEMENTS

Olof Akre – Supervisor, friend, former roommate at Danderyd Hospital and former floorball companion. Apart from general epidemiology, specific epidemiology and cancer epidemiology - for teaching me that a deadline is far away as long as there are seconds left. Thank you for all discussions and numerous coffee breaks we have had.

Pär Stattin – Co-supervisor and co-author. Thank you for your support, knowledge, experience in register-based research and, not a least, lightning fast email replies.

Ola Bratt – Co-author. For your excellent support and experience as scientist and urologist.

Stefan Nilsson – For being my mentor.

Tobias Nordström – Colleague, friend and co-author. For always being enthusiastic, no matter how bad the results fit the theory.

Erik von Seth – For being my close partner at the first scientific steps in Uppsala 2003. From thereafter, being a close friend.

Gustaf Håkansson – For being a close friend and partner at KI Epi School. And yup! You're next!

Fredrik Levin – my encouraging boss and head of the Urology Unit at Danderyd Hospital who, apart from giving me time to finish the thesis, showed me that the good things in life can be the simple things – watching birds and operate kidneys.

Mudhar Hasan – former head of the Urology Unit at Danderyd Hospital, who pulled me back to urology after five years of aimless wandering on the fields of general surgery.

Fredrik Hjern – for doing me the honour of being chairman of the dissertation and fellow of the Left-handed Surgeons Club.

Hans Garmo – Co-author of Paper I. For expert statistical knowledge and giving me inspiration to start using R.

Linda Drevin – Co-author of Paper II. For helping me in the struggle with imputation and polychoric correlations.

Folke Folkvaljon – Co-author of Paper III. For brilliant statistical help.

Thomas Frisell – Co-author. For unknowingly have inspired me to Paper II and introducing me to twin studies.

All participants of KI Epi school 2011-2013

Colleagues at the Department of Surgery and Urology at Danderyd Hospital

Ann-Christine and *Bernt Jansson* – my fans, my sponsors and my parents

Magnus, Anna, Ester and *Walter* – my dear brother and his family

Therese, Bertil and *Märta* – my beloved family

9 REFERENCES

[1]   NORDCAN n.d. https://www-dep.iarc.fr/nordcan (accessed October 19, 2020).

[2]   Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53. doi:10.1002/ijc.31937.

[3]   Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8. doi:10.1056/NEJMoa0810084.

[4]   ISHKININ Y, ZHYLKAIDAROVA A, NURGALIYEV N, AUYEZOVA E, OSHIBAYEVA A, GORBUNOVA N. Population-based Prostate Cancer Screening in Kazakhstan. Iranian Journal of Public Health 2017;46:917–22.

[5]   Nacusi LP, Tindall DJ. Targeting 5α-reductase for prostate cancer prevention and treatment. Nature Publishing Group 2011;8:378–84. doi:10.1038/nrurol.2011.67.

[6]   Buschemeyer WC, Freedland SJ. Obesity and prostate cancer: epidemiology and clinical implications. 2007;52:331–43. doi:10.1016/j.eururo.2007.04.069.

[7]   Cuzick J, Thorat MA, Andriole G, Brawley OW, Brown PH, Culig Z, et al. Prevention and early detection of prostate cancer. Lancet Oncol 2014;15:e484–92. doi:10.1016/S1470-2045(14)70211-6.

[8]   Hrbacek J, Urban M, Hamsikova E, Tachezy R, Heracek J. Thirty years of research on infection and prostate cancer: no conclusive evidence for a link. A systematic review. Urol Oncol 2013;31:951–65. doi:10.1016/j.urolonc.2012.01.013.

[9]   Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep 1966;50:125–8.

[10]   Epstein JI, Allsbrook WCJ, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma 2005;29:1228–42.

[11]   Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. 2015;40:1–252. doi:10.1097/PAS.0000000000000530.

[12]   Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. Jama 2005;293:2095–101. doi:10.1001/jama.293.17.2095.

[13]   Cuzick J, Fisher G, Kattan MW, Berney D, Oliver T, Foster CS, et al. Long-term outcome among men with conservatively treated localised prostate cancer. Br J Cancer 2006;95:1186–94. doi:10.1038/sj.bjc.6603411.

[14]   Akre O, Garmo H, Adolfsson J, Lambe M, Bratt O, Stattin P. Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBaSe Sweden. 2011;60:554–63. doi:10.1016/j.eururo.2011.05.047.

[15]   D'Amico AV, Whittington R, Malkowicz SB, Schnall M, Tomaszewski J, Schultz D, et al. A multivariable analysis of clinical factors predicting for pathological features associated with local failure after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 1994;30:293–302. doi:10.1016/0360-3016(94)90007-8.

[16]   Naji L, Randhawa H, Sohani Z, Dennis B, Lautenbach D, Kavanagh O, et al. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis. Ann Fam Med 2018;16:149–54. doi:10.1370/afm.2205.

[17]   Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40. doi:10.1016/j.eururo.2015.08.052.

[18]   ClinicalTrials.gov n.d.

[19]   Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 2017.

[20]   Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751–6. doi:10.1111/j.1464-410X.2005.05394.x.

[21]   D'Amico AV, Whittington R, Malkowicz SB, al E. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama 1998;280:969–74.

[22]   Guidelines on Prostate Cancer. Uroweborg n.d. http://www.uroweb.org/gls/pdf/08%20Prostate%20Cancer_LR%20March%2013th% 202012.pdf (accessed January 23, 2013).

[23]   auanet.org. n.d. https://www.auanet.org (accessed October 13, 2020).

[24]   NCCN.org. WwwNccnorg n.d. https://www.nccn.org/ (accessed September 27, 2017).

[25]   Bratt O, Folkvaljon Y, Loeb S, Klotz L, Egevad L, Stattin P. Upper limit of cancer extent on biopsy defining very low-risk prostate cancer. BJU Int 2015;116:213–9. doi:10.1111/bju.12874.

[26]   Gnanapragasam VJ, Lophatananon A, Wright KA, Muir KR, Gavin A, Greenberg DC. Improving Clinical Risk Stratification at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. PLoS Med 2016;13:e1002063. doi:10.1371/journal.pmed.1002063.

[27]   Gnanapragasam VJ, Bratt O, Muir K, Lee LS, Huang HH, Stattin P, et al. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. BMC Med 2018;16:31–10. doi:10.1186/s12916-018-1019-5.

[28]   Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 2011;117:5039–46. doi:10.1002/cncr.26169.

[29]   Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. Journal of Urology 2003;170:1798–803. doi:10.1097/01.ju.0000091805.98960.13.

[30]   Zelic R, Garmo H, Zugna D, Stattin P, Richiardi L, Akre O, et al. Predicting Prostate Cancer Death with Different Pretreatment Risk Stratification Tools: A Head-to-head Comparison in a Nationwide Cohort Study. 2020;77:180–8. doi:10.1016/j.eururo.2019.09.027.

[31]   Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. Nat Rev Genet 2013;14:139–49. doi:10.1038/nrg3377.

[32]   Richard S, Gardie B, Couvé S, Gad S. Von Hippel-Lindau: how a rare disease illuminates cancer biology. Semin Cancer Biol 2013;23:26–37. doi:10.1016/j.semcancer.2012.05.005.

[33]   Salomé JV. Clinical aspects of Lynch syndrome 2020.

[34]   Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al. Multiple Endocrine Neoplasia Type 1. The Journal of Clinical Endocrinology & Metabolism 1993;97:2990–3011. doi:10.1210/jc.2012-1230.

[35]   Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al. Multiple Endocrine Neoplasia Type 2 1993.

[36]   Carr S, Kasi A. Familial Adenomatous Polyposis 2020.

[37]   Meikle AW, Smith JA, West DW. Familial factors affecting prostatic cancer risk and plasma sex-steroid levels. Prostate 1985;6:121–8. doi:10.1002/pros.2990060202.

[38]   Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol 2011. doi:10.1007/s00345-011-0801-1.

[39]   Albright F, Stephenson RA, Agarwal N, Teerlink CC, Lowrance WT, Farnham JM, et al. Prostate cancer risk prediction based on complete prostate cancer family history. Prostate 2015;75:390–8. doi:10.1002/pros.22925.

[40]   EAU Guidelines on Prostate Cancer. 2020.

[41]   Gronberg H, Damber L, Damber JE. Studies of genetic factors in prostate cancer in a twin population. J Urol 1994;152:1484–7; discussion1487–9.

[42]   Page WF, Braun MM, Partin AW, Caporaso N, Walsh P. Heredity and prostate cancer: a study of World War II veteran twins. Prostate 1997;33:240–5. doi:10.1002/(SICI)1097-0045(19971201)33:4<240::AID-PROS3>3.0.CO;2-L.

[43]   Visscher PM, Hill WG, Wray NR. Heritability in the genomics era — concepts and misconceptions. Nat Rev Genet 2008;9:255–66. doi:10.1038/nrg2322.

[44]   Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85. doi:10.1056/NEJM200007133430201.

[45]   Hjelmborg JB, Scheike T, Holst K, Skytthe A, Penney KL, Graff RE, et al. The heritability of prostate cancer in the nordic twin study of cancer. Cancer Epidemiol Biomarkers Prev 2014;23:2303–10. doi:10.1158/1055-9965.EPI-13-0568.

[46]   Eeles RA, Olama Al AA, Benlloch S, Saunders EJ. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nature 2013;45:385–91–391e1–2. doi:10.1038/ng.2560.

[47]   Schumacher FR, Olama Al AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet 2018;50:928–36. doi:10.1038/s41588-018-0142-8.

[48]   Choudhury AD, Eeles R, Freedland SJ, Isaacs WB, Pomerantz MM, Schalken JA, et al. The Role of Genetic Markers in the Management of Prostate Cancer 2012;62:577–87. doi:10.1016/j.eururo.2012.05.054.

[49]   Netto GJ, Eich M-L, Varambally S. Prostate Cancer: An Update on Molecular Pathology with Clinical Implications. European Urology Supplements 2017;16:253–71. doi:10.1016/j.eursup.2017.10.001.

[50]   Benafif S, Kote-Jarai Z, Eeles RA, PRACTICAL Consortium. A Review of Prostate Cancer Genome-Wide Association Studies (GWAS). Cancer Epidemiol Biomarkers Prev 2018;27:845–57. doi:10.1158/1055-9965.EPI-16-1046.

[51]   Heidegger I, Tsaur I, Borgmann H, Surcel C, Kretschmer A, Mathieu R, et al. Hereditary prostate cancer - Primetime for genetic testing? Cancer Treat Rev 2019;81:101927. doi:10.1016/j.ctrv.2019.101927.

[52]   Witte JS, Mefford J, Plummer SJ, Liu J, Cheng I, Klein EA, et al. HOXB13 mutation and prostate cancer: studies of siblings and aggressive disease. Cancer Epidemiol Biomarkers Prev 2013;22:675–80. doi:10.1158/1055-9965.EPI-12-1154.

[53]   Nyberg T, Govindasami K, Leslie G, Dadaev T, Bancroft E, Ni Raghallaigh H, et al. Homeobox B13 G84E Mutation and Prostate Cancer Risk. 2018. doi:10.1016/j.eururo.2018.11.015.

[54]   Storebjerg TM, Høyer S, Kirkegaard P, Bro F, LuCamp Study Group, Ørntoft TF, et al. Prevalence of the HOXB13 G84E mutation in Danish men undergoing radical prostatectomy and its correlations with prostate cancer risk and aggressiveness. BJU Int 2016;118:646–53. doi:10.1111/bju.13416.

[55] Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8. doi:10.1056/NEJM199705153362001.

[56] Hawsawi YM, Al-Numair NS, Sobahy TM, Al-Ajmi AM, Al-Harbi RM, Baghdadi MA, et al. The role of BRCA1/2 in hereditary and familial breast and ovarian cancers. Mol Genet Genomic Med 2019;7:e879. doi:10.1002/mgg3.879.

[57] Nyberg T, Frost D, Barrowdale D, Evans DG, Bancroft E, Adlard J, et al. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. 2020;77:24–35. doi:10.1016/j.eururo.2019.08.025.

[58] Abdel-Rahman O. Evaluating Family History Links between Breast Cancer and Prostate Cancer Among PLCO Trial Participants. Clin Breast Cancer 2020;20:300–6. doi:10.1016/j.clbc.2020.03.005.

[59] Choi M, Kipps T, Kurzrock R. ATM Mutations in Cancer: Therapeutic Implications. Mol Cancer Ther 2016;15:1781–91. doi:10.1158/1535-7163.MCT-15-0945.

[60] AlDubayan SH, Pyle LC, Gamulin M, Kulis T, Moore ND, Taylor-Weiner A, et al. Association of Inherited Pathogenic Variants in Checkpoint Kinase 2 (CHEK2) With Susceptibility to Testicular Germ Cell Tumors. JAMA Oncol 2019;5:514–22. doi:10.1001/jamaoncol.2018.6477.

[61] Southey MC, Goldgar DE, Winqvist R, Pylkäs K, Couch F, Tischkowitz M, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. Journal of Medical Genetics 2016;53:800–11. doi:10.1136/jmedgenet-2016-103839.

[62] Zlowocka-Perlowska E, Narod SA, Cybulski C. CHEK2 Alleles Predispose to Renal Cancer in Poland. JAMA Oncol 2019;5:576. doi:10.1001/jamaoncol.2019.0022.

[63] Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. Risk of Prostate Cancer Associated With Familial and Hereditary Cancer Syndromes. J Clin Oncol 2020;38:1807–13. doi:10.1200/JCO.19.02808.

[64] Haraldsdottir S, Hampel H, Wei L, Wu C, Frankel W, Bekaii-Saab T, et al. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16:553–7. doi:10.1038/gim.2013.193.

[65] Ficarra V, Novara G, Rosen RC, Artibani W, Carroll PR, Costello A, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. 2012;62:405–17. doi:10.1016/j.eururo.2012.05.045.

[66] Matzinger O, Duclos F, van den Bergh A, Carrie C, Villà S, Kitsios P, et al. Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. Eur J Cancer 2009;45:2825–34. doi:10.1016/j.ejca.2009.07.009.

[67] Bul M, van den Bergh RCN, Zhu X, Rannikko A, Vasarainen H, Bangma CH, et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. BJU Int 2012;110:1672–7. doi:10.1111/j.1464-410X.2012.11434.x.

[68] Thomsen FB, Brasso K, Klotz LH, Røder MA, Berg KD, Iversen P. Active surveillance for clinically localized prostate cancer--a systematic review. J Surg Oncol 2014;109:830–5. doi:10.1002/jso.23584.

[69] Vellekoop A, Loeb S, Folkvaljon Y, Stattin P. Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. J Urol 2014;191:350–7. doi:10.1016/j.juro.2013.09.034.

[70] Yang DD, Mahal BA, Muralidhar V, Nezolosky MD, Vastola ME, Labe SA, et al. Risk of Upgrading and Upstaging Among 10 000 Patients with Gleason 3+4

Favorable Intermediate-risk Prostate Cancer. Eur Urol Focus 2017. doi:10.1016/j.euf.2017.05.011.

[71]   Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, et al. Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. BJU Int 2018;122:59–65. doi:10.1111/bju.14166.

[72]   MD PHG, MD JA, MD MA, MD TN, MD PPW, PhD PYB, et al. Articles Prostate cancer screening in men aged 50–69 years(STHLM3): a prospective population-based diagnostic study. Lancet Oncology 2015:1–10. doi:10.1016/S1470-2045(15)00361-7.

[73]   Bratt O, Garmo H, Adolfsson J, Bill-Axelson A, Holmberg L, Lambe M, et al. Effects of prostate-specific antigen testing on familial prostate cancer risk estimates. J Natl Cancer Inst 2010;102:1336–43. doi:10.1093/jnci/djq265.

[74]   Lindström LS, Hall P, Hartman M, Wiklund F, Grönberg H, Czene K. Familial concordance in cancer survival: a Swedish population-based study. Lancet Oncol 2007;8:1001–6. doi:10.1016/S1470-2045(07)70282-6.

[75]   Hemminki K, Ji J, Försti A, Sundquist J, Lenner P. Concordance of survival in family members with prostate cancer. J Clin Oncol 2008;26:1705–9. doi:10.1200/JCO.2007.13.3355.

[76]   Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members 2010;58:275–80. doi:10.1016/j.eururo.2010.02.002.

[77]   Brandt A, Sundquist J, Hemminki K. Risk for incident and fatal prostate cancer in men with a family history of any incident and fatal cancer. 2012;23:251–6. doi:10.1093/annonc/mdr056.

[78]   Guidelines - American Urological Association. Auanetorg n.d. https://www.auanet.org/guidelines (accessed October 13, 2020).

[79]   Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27–33. doi:10.1080/02841860802247664.

[80]   Nilsson M, Tavelin B, Axelsson B. A study of patients not registered in the Swedish Cancer Register but reported to the Swedish Register of Palliative Care 2009 as deceased due to cancer. Acta Oncol 2014;53:414–9. doi:10.3109/0284186X.2013.819115.

[81]   Nationella Prostatacancerregistret n.d. npcr.se (accessed September 27, 2017).

[82]   Tomic K, Berglund A, Robinson D, Hjälm-Eriksson M, Carlsson S, Lambe M, et al. Capture rate and representativity of The National Prostate Cancer Register of Sweden. Acta Oncol 2015;54:158–63. doi:10.3109/0284186X.2014.939299.

[83]   Ekbom A. The Swedish Multi-generation Register. Methods Mol Biol 2011;675:215–20. doi:10.1007/978-1-59745-423-0_10.

[84]   Lichtenstein P, De faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies 2002;252:184–205. doi:10.1046/j.1365-2796.2002.01032.x.

[85]   Svenska Tvillingregistret, världens största tvillingregister. KiSe n.d. http://ki.se/forskning/svenska-tvillingregistret (accessed September 27, 2017).

[86]   Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32:765–73. doi:10.1007/s10654-017-0316-1.

[87]   Dödsorsaksstatistik. Historik, produktionsmetoder och tillförlitlighet 2010:1–38.

[88]   Fall K, Strömberg F, Rosell J, Andrèn O, Varenhorst E, South-East Region Prostate Cancer Group. Reliability of death certificates in prostate cancer patients. Scand J Urol Nephrol 2008;42:352–7. doi:10.1080/00365590802078583.

[89]   Hagel E, Garmo H, Bill-Axelson A, Bratt O, Johansson JE, Adolfsson J, et al. PCBaSe Sweden: a register-based resource for prostate cancer research. Scand J Urol Nephrol 2009;43:342–9. doi:10.3109/00365590903024577.

[90]   Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Third edition. Lippincott Williams & Wilkins; n.d.

[91]   Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20:40–9. doi:10.1002/mpr.329.

[92]   Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91. doi:10.1016/j.jclinepi.2006.01.014.

[93]   Morisot A, Bessaoud F, Landais P, Rébillard X, Trétarre B, Daurès J-P. Prostate cancer: net survival and cause-specific survival rates after multiple imputation. BMC Medical Research Methodology 2015;15:1–14. doi:10.1186/s12874-015-0048-4.

[94]   Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. Eur J Epidemiol 2014;29:551–8. doi:10.1007/s10654-013-9873-0.

[95]   Deibel TL, Sommers BD, Gilmore R, Sagalowsky A, Shore N. Talking to patients about risk. Urol Oncol 2007;25:348–50. doi:10.1016/j.urolonc.2007.05.005.

[96]   Statistiska Centralbyrån n.d. https://www.scb.se (accessed October 19, 2020).

[97]   Nationella Kvalitetsregister n.d. https://kvalitetsregister.se (accessed October 19, 2020).

[98]   Gandaglia G, Bray F, Cooperberg MR, Karnes RJ, Leveridge MJ, Moretti K, et al. Prostate Cancer Registries: Current Status and Future Directions. Eur Urol 2016;69:998–1012. doi:10.1016/j.eururo.2015.05.046.

[99]   PIONEER n.d. https://prostate-pioneer.eu (accessed October 19, 2020).