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Prostate Cancer

Familial Risks in 317 000 Patients With Prostate Cancer in Relation to Metastases and Survival-Guiding Diagnostics

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Abstract

Background: Swedish nationwide family and cancer data offer the largest global resource for study of familial cancer. We focus here on familial risks in prostate cancer (PC) with questions on risk in individuals from families of multiple affected members and association of familial risk with metastatic disease and survival.
Methods: Familial relative risk of PC was estimated using standardized incidence ratios (SIRs) for second-generation men with a father or brother affected with PC, considering distinct groups by number and type of affected relatives.
Results: Familial SIRs ranged from 2.22 (2 brothers with PC) to 11.5 (≥5 brothers with PC). The proportions of affected men increased from about 15% (2-case families) to 50% (≥5-case families). Age-incidence curves showed successively higher rates for men from multi-case families. Older patients with PC had the highest proportion of metastases at diagnosis, but in each age group, familial patients presented with a lower proportion of metastases compared with nonfamilial cases. Among brothers, the proportion of metastasis was higher in brothers first diagnosed compared with brothers with subsequent diagnosis. Survival in familial cases was better compared with nonfamilial cases among patients without metastases. Among such patients, brothers diagnosed first survived worse than subsequent brothers.
Conclusions and clinical implications: The largest family study yet conducted on PC was based on 34 468 familial cases. Risk varied greatly by family constellations, emphasizing the need for a detailed family history at diagnosis as basis for clinical decision-making and genetic counseling. The reported high risks should encourage implementation of familial risk into schemes for PC screening.

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Patient summary: Patients with prostate cancer often have a relative who has prostate cancer. When PC is diagnosed, it is important that the patient reports a reliable history of relatives earlier diagnosed with PC. It may influence his treatment.

1. Introduction

Family history of cancer implies that blood relatives have been diagnosed with the same cancer. It can be considered between first-degree relatives (FDRs; parents, offspring, or siblings) or more distant relatives with the distinction that sharing of genes and environmental risk factors is diluted between distant relatives. Among cancers, prostate cancer (PC) has the highest familial proportion, which was 26% among FDRs in Sweden, far higher than that for female breast (18%) or colorectal (16%) cancer [1]. Familial relative risk is another measure used in family studies; for the previously mentioned cancers, it was 2.0 for FDRs and increased when several family members are affected [1].

The epidemiology of PC changed drastically in Sweden and in many other European countries starting in about 1990 with the introduction of prostate-specific antigen (PSA) testing [2]; the consequence was that the incidence of PC doubled [3]. The changes also included earlier diagnostic age and shifting of the diagnostic presentation—tumor, node, metastasis (TNM)—toward less malignant forms [4]. The diagnostic pathway for PC has continued to evolve since the introduction of PSA toward increasing use of prostate magnetic resonance imaging (MRI) and MRI-targeted biopsies, leading to a higher detection of small volume significant cancers. The intermediate risk category (T1–2, Gleason 7, and/or PSA between 10 and 20 ug/L) has become the largest category in Sweden, encompassing close to 40% of all cases in 2023 (https://npcr.se/wp-content/uploads/2024/09/20240924_npcr_nationell_rapport_2023.pdf). Most likely the diagnosis of familial PC was affected; it has been reported that diagnosis of PC in first brother led to a transient increase in diagnoses of PC, particularly of PSA-detected PC in subsequent brothers [5,6].

We used Swedish nationwide data identified through the national cancer registry covering essentially complete families among 16 million individuals with cancer from 1958 onward [7]. Several previous family studies on PC have been published from earlier versions of the dataset, including, more recently, a risk prediction modeling [8–12]. Using these data up to the year 2021, we focus here on analysis of familial risks in PC in men in the second generation (born after 1931) and their multiple FDRs diagnosed with PC. We further show a negative association with family history and metastatic disease which also influences survival in PC. Although mortality in PC has decreased, diagnosis and treatment cause harm to patients motivating continuous striving for better risk-adapted management [13].

2. Materials and methods

The analyzed dataset originates from the latest update of the Swedish Cancer Registry (covering period 1958–2021), linked to the Multigeneration Register Supplementary Table 1.

All risk calculations were based on the brothers in the second generation using the cohort method as described [14]. Patients with PC in generation 1 were included as probands who did not contribute to the person-year calculation. The calculation was based on the standardized incidence ratio (SIR) as the ratio of the observed number of PCs in men with specified number of relatives with PC, compared with expected number of PCs considering person-years at risk. In families with one or more brothers with PC, the affected and the unaffected brothers contributed person-years to different risk groups, as the number of their brothers with PC differed. The reference incidence rates were calculated for men whose FDRs were not diagnosed with PC. For each risk group, the proportions of affected members were calculated by dividing the number of diagnosed cases by the numbers of individuals at risk in that type of family, considering men in the second generation.

The follow-up started on date of birth or beginning of the study (1 January 1961), whichever came later. The follow-up was terminated at the time of death, emigration, PC diagnosis, or end of study (29 December 2021), whichever came earliest. The rates were standardized based on family size (number of brothers in family), age (5-year groups), calendar period (5-year groups), educational level (<9 y, 9 y, 10–11 y, 12 y, college <3 y, university graduate, postgraduate) and geographic region (north, south, and three largest cities). The 95% confidence intervals (CIs) were calculated assuming that observed rates follow Poisson distribution.

Throughout the manuscript, groups with estimated SIRs, incidence rates and cumulative incidence, were labeled by total number of patients with PC that would result if the followed person (case) was diagnosed with PC. Therefore, "2 brothers with PC" designates risk and incidence estimates for men with one brother proband diagnosed with PC.

The TNM staging system, including T1c (nonpalpable prostate tumor detected by PSA) and metastatic M stages were systematically available in the Cancer Registry since 2004. Since 2010, the Cancer Registry implemented the 7th TNM Edition, leading to elimination of code Mx (metastases not determined) and all cases where metastases could not be confirmed were coded M0. The analyses of association between family history and metastasis and family history and survival were performed on cases covering years 2004–2021, where among 180 795 PCs, M data were missing for 5921 cases.

The probability of de novo metastasis was modeled using generalized estimating equations multivariable model with logit link function, accounting for correlation between brothers (using exchangeable correlation structure with

robust variance estimation). The predictors in the model included family history, age at diagnosis, and diagnostic year.

Survival was analyzed by Cox proportional hazards model with 95% CIs in 10-y follow-up periods. The included predictors were family history, age (time-varying covariate), presence of metastasis and calendar year. The nonlinear effect of age was modeled using natural cubic splines with two degrees of freedom. A three-way interaction was included to allow for the nonlinear age–hazard relationship to differ by family history and metastatic status. Additionally, we fitted separate Cox models, stratifying by metastatic status and diagnostic age (split at median diagnostic age), adjusting for age (separate baseline hazard for different groups by diagnostic age, in addition to linear effect of age at diagnosis) and calendar year of diagnosis (linear effect). The follow-up started at diagnosis and ended with death (the event of interest) or with censoring. The observations were censored at first occurrence: emigration, end of study period (29 December 2021), or end of 10-y follow-up period. The regression models (metastasis prediction and survival analysis) were limited to families with up to two brothers with PC to ensure robust case numbers and interpretability.

All statistical analyses and data visualization were done using SAS and R (version 4.4.0).

Some further details of methods are included in the Supplement.

3. Results

3.1. 60-Year incidence and mortality trends in PC in Sweden

Age-standardized incidence data for PC were available from 1965 onward in diagnostic age groups from the NORDCAN database (Fig. 1A). In all age groups at ≥60 y, there was a modest increase in rates to about 1990 when the trend shifted upward, particularly in age groups 60–75 y. The steepest increase was in age group 65–69 y, as the incidence doubled in a 10-year period. The increasing trends culminated first in the oldest age groups around year 2000. In age groups <70 y, the incidence stayed at the level of 2005. Mortality trends were followed from 1955 (Fig. 1B). In the oldest age groups, mortality increased until 1975 and then declined in two waves, the largest after 2000; this decline was observed in all age groups. Notably, the mortality/incidence ratio became favorable toward the end of the study due to the fast decline in mortality.

3.2. Numbers of patients with PC in FDRs and familial risks

Population characteristics of the three-generation national data are shown in Supplementary Table 1.

We present familial risk calculations considering two generations, resembling the clinical setting (Table 1). An additional reason for not considering men in the third generation was their young age and thus their total number of PCs of only 7917. Familial risks were calculated for men in generation 2 considering PCs in their brothers and fathers. Among 34 468 familial cases, SIRs increase stepwise from two, three, four, and ≥5 affected brothers from 2.22 to 4.11, 6.23, and 11.5. If a father was affected, the SIRs for sons increased from 1.88 (one son with PC) to 10.9 (≥4 sons with PC). Case numbers decreased almost by a factor of 10 for brothers and of five for father–sons by family type. The proportions of affected cases in each family type increased from about 15% stepwise to 50%, with an overall percentage of 17.

3.3. Age-specific familial and cumulative incidence

We wanted to compare incidence rates in the second generation depending on the number of affected FDRs in any of the three generations (Fig. 2A). The reference (one case in a family) incidence rate reached a maximum at age 75–

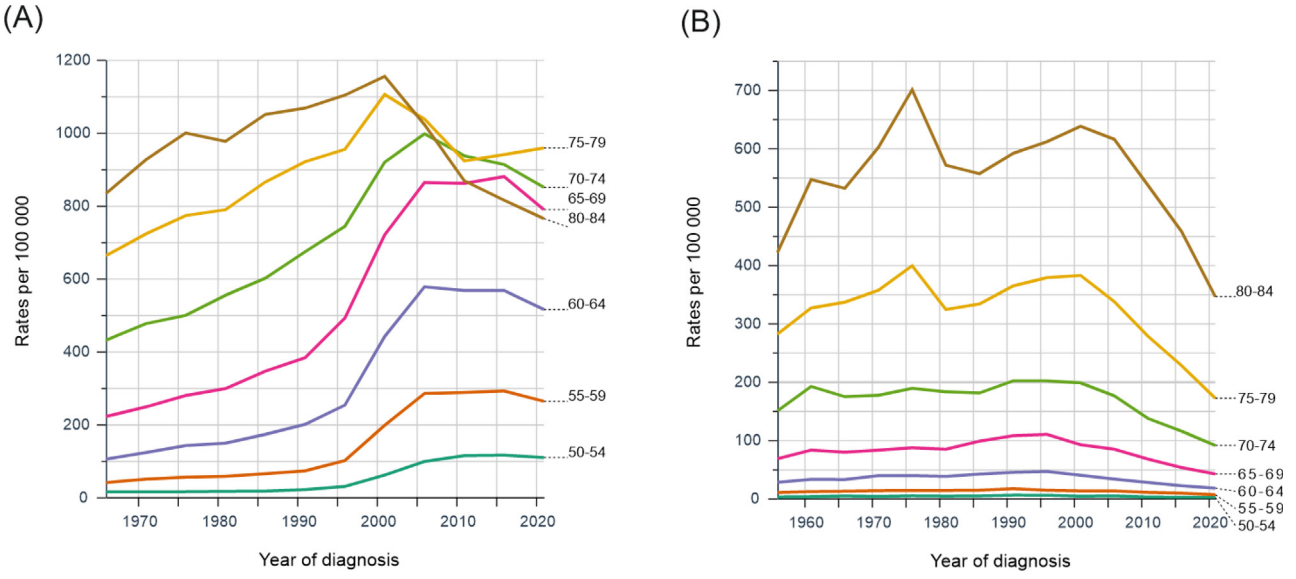

Fig. 1 – Age-standardized Swedish incidence (A, from 1965) and mortality (B, from 1955) trends for PC in 5-year age-groups. Data were obtained from the NORDCAN database through the International Agency for Cancer web Global Cancer Observatory.

Table 1 – SIR for PC in second generation (listed on first column) based on family history defined by number of family members affected with PC among brothers (top) and sons of affected fathers (bottom), adjusted for family size. *N* at risk is the number of men with a respective family history who contributed person-years for SIR calculation

Family members with PC by generation					
2nd	1st	*N* at riskgeneration 2	*N* familialgeneration 2	Proportion affected (%)[a]	SIR [95% CI]
2	0	73 481	12 720	17	2.22 [2.18–2.26]
3	0	6870	1858	27	4.11 [3.92–4.30]
4	0	842	287	34	6.23 [5.53–6.99]
5+	0	199	89	45	11.5 [9.24–14.2]
1	1	106 562	15 087	14	1.88 [1.85–1.91]
2	1	14 030	3662	26	3.81 [3.69–3.94]
3	1	1806	592	33	5.63 [5.19–6.10]
4+	1	349	173	50	10.9 [9.35–12.7]
Total		204 139	34 468	17	

[a] Proportion affected: % of *N* affected of *N* at risk.

79 y; in multi-case families the maxima of the curves shifted stepwise to lower ages, reaching 65–69 y for men with ≥4 affected FDRs. Cumulative incidence for the same dataset is shown in Fig. 2B. A stepwise increase by increasing number of affected brothers led to a cumulative incidence increase by age 90 y from 0.15 to 0.6.

3.4. *Familial risk, metastatic disease, and survival*

Whether family history (through fathers or brothers) may be associated with metastatic disease, we compared patients with PC at various age groups depending on family history (Fig. 3A). The proportion of de novo metastases (metastasis at diagnosis, M1) increased by age, and in each age group, familial cases showed a lower proportion of metastases compared with those lacking family history. The difference was largest in patients diagnosed at age <50 y (2.5-fold). The most likely reason for the lower proportion of metastases among familial cases was earlier diagnosis in familial cases. In a brothership, the metastatic proportion was higher in the brother diagnosed first, compared with the subsequent brothers diagnosed after him (Fig. 3B).

High age was a strong predictor of de novo metastases (odds ratio [OR] for ≥80 y-old men 3.61) (Table 2). In families with up to two affected brothers, the OR for the first affected brother in a brothership was slightly above 1.00, but for the subsequent brother it was 0.72 (95% CI: 0.63–0.82); for son of an affected father it was 0.90 (95% CI: 0.83–0.98) and for subsequent brother with an affected father it was 0.60 (95% CI: 0.46–0.78). The OR declined (0.96) for every passing year.

Survival by family history and de novo metastasis was analyzed in a Cox proportional hazards model with 95% CIs, considering various familial constellations (Fig. 4). Men without a family history were the reference group with hazard ratio [HR] = 1.00. In brothers without de novo metastasis, HR for the second brothers was lower than that for the first brother up to a diagnostic age of about 75 y (Fig. 4A). HRs for sons of affected fathers started from HR of 0.6 age 55 y and reached HR of 1.00 at age past 80 y (Fig. 4B). In the metastatic group, HR for second affected brother remained below 1.00 even at advanced age, but the variance was large due to lower case numbers (Fig. 4C). In men with a metastatic disease, the paternal history was not associated with significant survival benefit at any age (Fig. 4D).

Overall HRs by family history, including cases with both brother and father probands are shown in Supplementary Table 3. HR for second brother was 0.90 and for a son of an affected father it was 0.88. The lowest HR of 0.75 was for subsequent brother with an affected father. We further stratified analysis by diagnostic age (younger/older with cutoff at median = 67 y), which confirmed stronger contribution of a family history for subsequent brothers at younger age (HRs 0.74 vs 0.95 in nonmetastatic group). Case numbers for metastatic PC we low and the only significant HR of 0.81 (and 0.58 for diagnosis before age 68 y) was for subsequent brother.

4. Discussion

Family history and blood PSA levels are two important risk factors of PC [15]. Here we use a unique three-generation database on 317 000 medically diagnosed PCs from nationally registered family relationships [7]. A total of 34 500 patients with PC with affected FDRs were included. However, we did not use the relatively young third generation with low case numbers in analysis of familial risk because in the current clinical reality three-generation PC families are utterly rare. As comparison, a recent large United Kingdom study included 3871 patients with PC with affected FDRs [16]. The present results displayed variation of familial risks (ie, SIRs) among FDRs ranging from 2.22 to 11.5 among brothers, and from 1.88 to 10.9 among brothers with an affected father (Table 1). Overall, 17% of men in the second generation with a family history (brother or father) were diagnosed with PC during the present follow-up time. The proportion increased to about 50% when ≥5 FDRs were diagnosed with PC.

What are clinical implications of a confirmed familial risk? According to the cumulative incidence data of the present study (Fig. 2B), 12% of men were diagnosed with PC by age 80 y. When two, three, or four family members were diagnosed with PC, risk by 80 y reached 28%, 36%, and 43%. These risks can be compared to carriers of pathogenic mutations in the known highest-risk genes predisposing to PC, as cited by Finch, et al [17]: *BRCA2* 60%, *BRCA1* 29% and *HOXB13* variant G84E 60% all by age 85 y and *MSH2*

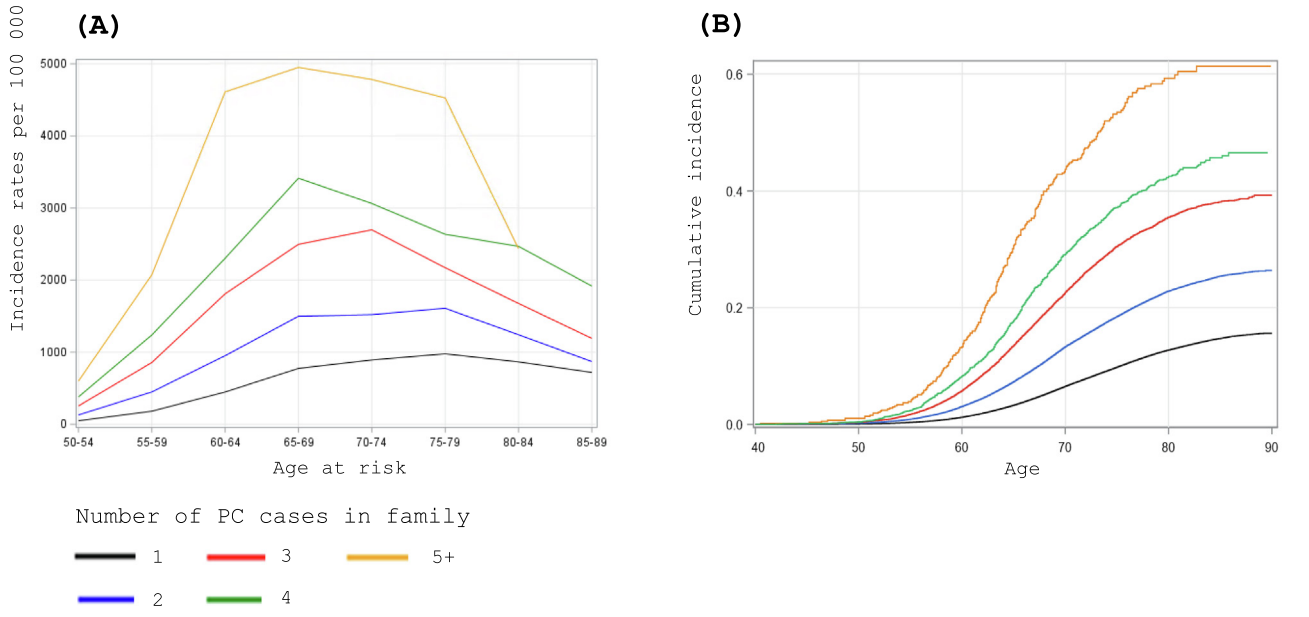

Fig. 2 – Age-specific incidence rate (A) and cumulative proportions (B) for PC followed since 40 y of age, depending on the number of affected FDRs in the family. Note the different Y-axis scales in (A) and (B).

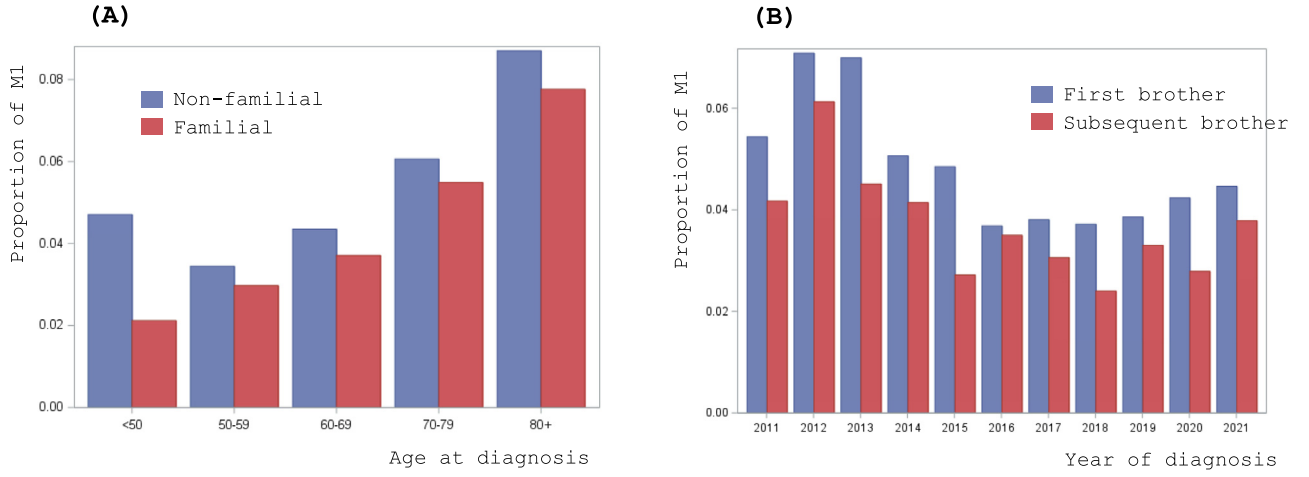

Fig. 3 – (A) The proportion of metastases at diagnosis (M1) in patients with PC at various age groups depending on family history in fathers and brothers. (B) The proportion of metastases at diagnosis among brothers over years since 2011.

24% by age 75 y. Clinical family histories should also consider diagnostic ages and go beyond FDRs and garner evidence about possible familial predisposition through any known male relatives. Judging from the previously mentioned cumulative incidence data in our family study, genetic testing would seem justified when a third FDR family member was diagnosed with PC. In general, knowing familial risks help patients and urologists plan individual risk-adapted strategies for PSA and MRI monitoring for willing patients [18]. High-risk patients might benefit from early onset and more rigorous follow-up, especially in the case of metastatic or advanced PC in the family [19].

The results offer empirical risk estimates useful for clinical counseling and screening [20]. At diagnosis of a patient with PC, the number and type of affected relatives will allow assessment of family history, which may be relatively reliable because of public discussion of PC has become commonplace. This has helped patients to be more open about their disease to the family members, instead of earlier feelings of shame and secrecy. Genetic counseling will evaluate family histories and may recommend genetic testing which may reveal mutations in genes predisposing to PC including *CHEK2*, *ATM2*, *BRCA2*, *HOXB13* and other mutations [19,21–23]. Loss-of-function variants in genes *ATM*, *BRCA2*, *MSH2*, and *NBN* have been found in aggressive PC [24]. However, contribution of social and life-style factors and even overdiagnosis may play a role [13,25].

Earlier data on mortality in familial PC have been inconsistent as reviewed by Brook et al [16]. Their own data showed significantly improved survival in familial PC, independent of TNM, Gleason, or PSA levels. Their conclusion was that reduced mortality was largely due to a greater

Table 2 – Prediction of de novo metastasis (M1) at time of PC diagnosis by age group, family history and calendar year (odds ratios derived by generalized estimating equations multivariable model with logit link function)

	N (N_{events})	OR [95% CI]
Age group, y		
50–59	17 564 (576}	1 ref.
<50	1447 (52)	1.16 [0.87–1.54]
60–69	55 568 (2320)	1.29 [1.18–1.42]
70–79	39 552 (2347)	2.07 [1.88–2.28]
80+	5107 (436)	3.61 [3.15–4.13]
Family history		
Nonfamilial	86 263 (4349)	1 ref.
First brother	5528 (311)	1.08 [0.96–1.22]
Second brother	6951 (257)	0.72 [0.63–0.82]
Son of father with PC	16 844 (692)	0.90 [0.83–0.98]
First brother, son of father with PC	1648 (65)	0.81 [0.63–1.04]
Second brother, son of father with PC	2004 (57)	0.60 [0.46–0.78]
Per passing year	119 238 (5731)	0.96 [0.95–0.96]

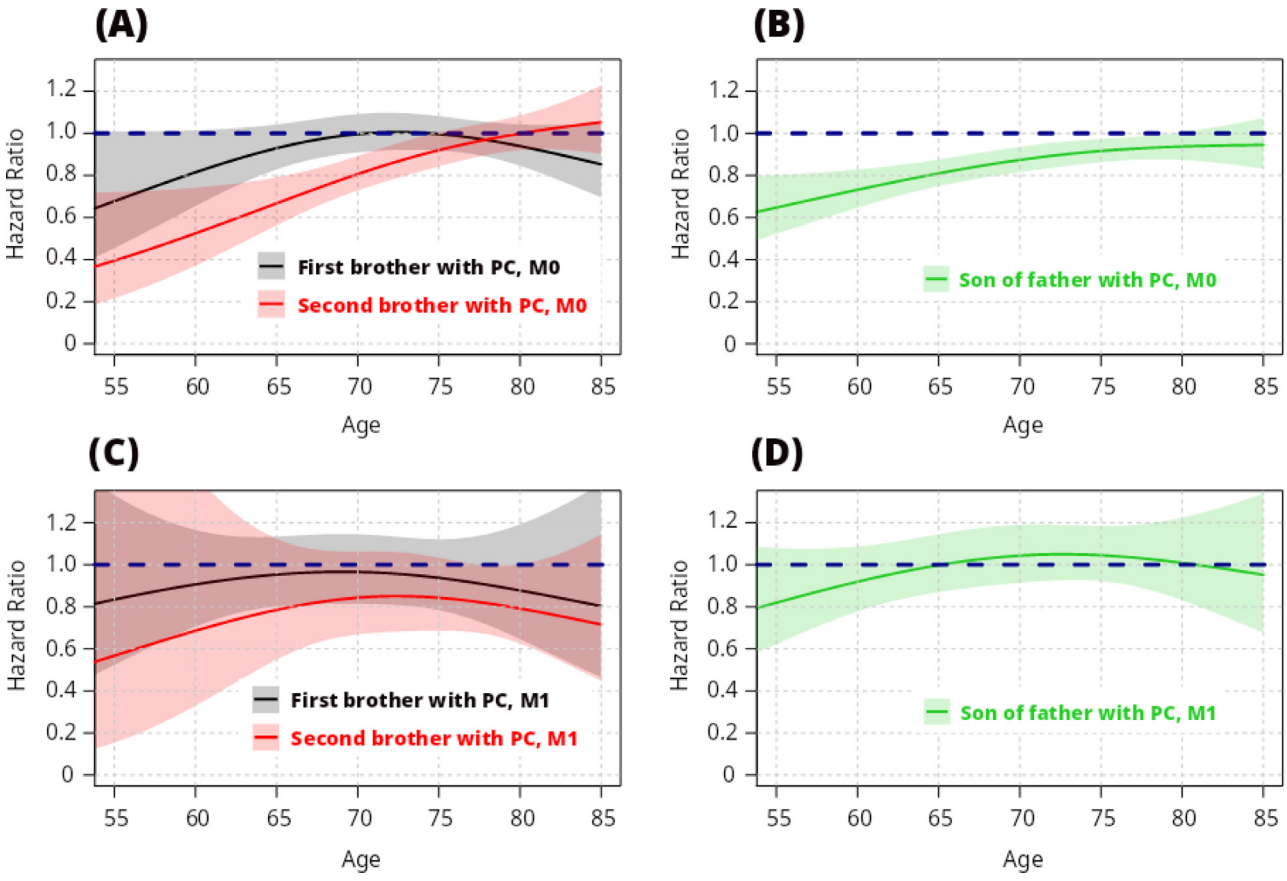

Fig. 4 – Hazard ratio for overall survival of men diagnosed with PC based on age, family history and metastatic status at diagnosis, evaluated with reference to nonfamilial cases and adjusted for calendar year. (A) First and second affected brother, without metastases. $N_{at\ risk}$ (N_{events}): first brother: 5043 (898), second brother: 6464 (896). (B) Sons of affected fathers, without metastases. $N_{at\ risk}$ (N_{events}): 15 526 (1733). (C) First and second affected brother, with metastases, $N_{at\ risk}$ (N_{events}): first brother: 301 (226), second brother: 252 (144). (D) Sons of affected fathers, with metastases $N_{at\ risk}$ (N_{events}): 668 (425).

awareness of the disease. However, the summary HR considering the published data was close to 1.00 [16]. The present results agree with the Brook et al data with significantly improved survival in familial cases (Fig. 4). We have earlier published survival data showing concordance of both good and poor survival in PC between fathers and sons [26].

We could suggest the likely reason for good survival of familial cases; they were diagnosed at an earlier stage of disease progression, indicated by their lower proportion of metastatic disease. This was observed in all diagnostic age groups with the largest difference in those diagnosed below age 50 y (Fig. 3A). The results showed further that among brothers, the proportion of metastasis was highest in the brothers first diagnosed (Fig. 3B). The likely explanation was the concern of the heathy brother after the first brother's diagnosis, followed by antedated medical contacts. In unfortunate cases he was diagnosed with PC; however, with

a less malignant disease compared to his brother. The lowest risk for metastatic disease (0.60) was observed for the subsequent brother with an affected father (Table 2). Not unexpectedly, such family relationships with lower metastatic burden are associated with improved survival (Supplementary Table 3). Using Cox proportional hazards model, we confirmed the survival advantage of sons of affected fathers and second affected brothers compared to nonfamilial cases without metastasis (Fig. 4), while no clear survival advantage was observed for first affected brothers.

So far, there are no generally accepted screening methods for PC. The European Association of Urology recommends risk-adapted strategies for well-informed men interested in a tailored approach for finding PC [18]. The available schemes usually start with a PSA test and then stratify patients into MRI and/or biopsy groups [27]. In Germany, the PROBASE trial is based on early (45 y) PSA determination and resulting risk stratification [28]; other modifications have been applied in the ongoing Swedish (Göteborg-2) and Finnish (ProScreen) trials [29,30]. Family history is normally not a part of risk stratification probably because it has been relatively rare, affecting old men, and reporting has not been reliable. However, in the PSA era PC diagnosis has shifted to earlier ages (Table 1) and PC has become the most common familial cancer [1].

The limitations of the study include availability of TNM data since 2004, the lack of detailed characteristics of the tumor (PSA level, Gleason score, and volume other than T stage), and absence of information regarding any treatment. As discussed previously, familial cases tend to be diagnosed early with favorable tumor characteristics; these contribute to the survival advantage, which we could not fully control. Additionally, familial risk is the aggregation of cases between family members, the causes of which may include genetic and complex social and environmental underpinnings. PSA screening belongs to these latter underpinning which influences familial risks between brothers but also between other family relationships [5,6,16].

In conclusion, this largest family study on PC yet conducted allowed us to establish familial risks in diverse family constellations, encompassing three generations of affected FDRs. The data lay out a solid basis for clinical risks assessment and management and emphasize further the need to carefully record family history at diagnosis of new cases [20,31]. As the screening programs for PC are evolving, family history should gain a place in risk stratification, the benefits of which could be quantified in screening trials considering different types of family constellations, distinguished by their prevalence and magnitude of risk.

Data availability: Anyone wishing to use these data should contact the National Board of Health and Welfare, Stockholm.

Ethics: The study was approved by the Swedish Ethical Review Authority (Reference 2021/05188 and subsequent amendments). Informed consent is by law not needed for use of national register data. The study was conducted in accordance with the Declaration of Helsinki.

Author contributions: Kari Hemminki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design: K Hemminki, O Hemminki.
Acquisition of data: K Sundquist, J Sundquist.
Analysis and interpretation of data: Zitricky, K Hemminki, O Hemminki, AK
Drafting of the manuscript: K Hemminki and all other authors.
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Zitricky, K Hemminki, Försti.
Obtaining funding: K Hemminki, K Sundquist, J Sundquist.
Administrative, technical, or material support: AHJ
Supervision K Hemminki
Other (*Approval of the final text*): All authors.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2026.03.006.

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