Familial risks in 317,000 prostate cancer patients in relation to metastases and survival guiding diagnostics

Kari Hemminki [1,2], Frantisek Zitricky [1], Kristina Sundquist [3,4,5], Jan Sundquist [3,4,5], Asta Försti [6,7], Akseli Hemminki [8,9], Otto Hemminki [9,10]

[1] Biomedical Center, Faculty of Medicine, Charles University, 30605 Pilsen, Czech Republic;
[2] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany;
[3] Center for Primary Health Care Research, Lund University, 205 02 Malmö, Sweden;
[4] University Clinic Primary Care, Skåne University Hospital, Region Skåne, Sweden;
[5] Department of Family and Community Medicine, McGovern Medical School, The University of Texas Health Science Center, Houston, Texas, USA;
[6] Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany;
[7] Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany;
[8] Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland
[9] Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki. Finland;
[10] Department of Urology, Helsinki University Hospital, Helsinki, Finland

Correspondence to:
Kari Hemminki
Biomedical Center, Faculty of Medicine, Charles University, 30605 Pilsen, Czech Republic.
Email: k.hemminki@dkfz.de

Words: 2940 (text), 249 (abstract).

Key words: familial risk, germline genetics, heredity, age of onset, early onset.

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 (standardized incidence ratio, SIR) was calculated to men in the second generation when their fathers, brothers or sons had PC.

Results: A large proportion (69.3%) of the families presented with a single man diagnosed with PC; the proportion of multi-case families declined from 24.6% (2 PCs), 5.1% (3 PCs) and 1.1% (4 or more PCs). Familial SIRs ranged from 1.88 (15,000 father-son pairs) to 41.8 (cases in three

generations). Age-incidence curves showed successively higher rates for men from multi-case families. Older PC patients had the highest proportion of metastases at diagnosis but in each age-group familial patients presented with a lower proportion of metastases compared to non-familial cases. Among brothers, the proportion of metastasis was higher in brothers first diagnosed compared to brothers with subsequent diagnosis. Men in multi-case families survived better than non-familial patients.

Conclusions and clinical implications: The largest family study yet conducted on PC found two or more affected cases in 35,200 families. 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.

Patient Summary:

Prostate cancer patients have often a relative who has prostate cancer. When prostate cancer is diagnosed it is important that the patient reports a reliable history of relatives earlier diagnosed with prostate cancer. It may influence his treatment.

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 26.4% among FDRs in Sweden, far higher than that for female breast (17.5%) or colorectal (15.7%) cancer (1). Familial relative risk is another measure used in family studies; for the above 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 about 1990 with the introduction of PSA testing (2); the consequence was that the incidence of PC doubled (3). The changes included also earlier diagnostic age and shifting of the diagnostic presentation (TNM) towards less malign forms (4). Diagnostic pathway for PC has kept on changing even after the introduction of PSA towards increasing use of prostate MRI and MRI targeted biopsies leading to 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 apply here Swedish nationwide data covering essentially complete families among 16 million individuals with cancers from 1958 onwards through the national cancer registry (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 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).

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**.

In analysis of familial relative risk, one person of each family diagnosed with PC in generation 2 was defined as case, and all other affected FDRs in the 3 generations were defined as probands. The calculation was based on the standardized incidence ratio (SIR) as the ratio of the observed number of PCs in population at risk (with family history) to the expected number of PCs (in those whose FDRs were not diagnosed with PC). The follow-up started on date of birth or beginning of the study (1st January 1961), whichever came later. The follow-up was terminated at time of death, emigration, PC diagnosis or end of study (29th December 2021), whichever came earliest. The rates were standardized based on sex, age (5-year groups), calendar period (5-year groups), educational level (<9 years, 9 years, 10-11 years, 12 years, college <3 years, university graduate, postgraduate) and geographic region (north, south and 3 largest cities). The 95% confidence intervals (CIs) were calculated assuming that observed rates follow Poisson distribution.

Throughout the manuscript, groups with estimated SIRs were labeled by total number of PC patients 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 (Tumor, Node, Metastasis) staging system, including T1c (non-palpable 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 analysis was limited to families with up to 2 brothers with PC to ensure robust case numbers. The reference was a man without family history. The probability of de novo metastasis was modelled using generalized estimating equations with logit link function, accounting for correlation between brothers. The predictors in the model included family history, age at

diagnosis and diagnostic year. Survival was analyzed by Cox proportional hazards models with 10 years follow-up, adjusting for age (separate baseline hazard for different age groups in addition to linear effect of diagnostic age) and calendar year of diagnosis (linear effect). The analysis was stratified by metastatic status and age group (split at median diagnostic age).

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

Some further details of methods are included in **Supplementary Methods**.

RESULTS

60-Year incidence and mortality trends in PC in Sweden

Age-standardized incidence data for PC were available from 1965 onwards in diagnostic age groups from the NORDCAN database (**Fig. 1A**). In all age groups at 60+ years there was a modest increase in rates to about 1990 when the trend shifted upwards particularly in age groups 60-75 years. The steepest increase was in age group 65-69 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 below 70 years the incidence stayed at the level of 2005. Mortality trends were followed from 1955 (**Fig. 1B**). In the oldest age groups mortality increased to 1975, and then declined in two waves, the largest after year 2000; this decline was observed in all age groups. Notably, the mortality/incidence ratio became favorable towards the end of the study due to the fast decline in mortality.

Numbers of PC patients in FDRs and familial risks

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

We present case numbers and familial risk in two generations, resembling the clinical setting **(Table 1).** Familial risks were calculated to men in generation 2 for which brothers were available and PCs in fathers were additionally considered. SIRs increase stepwise among 2, 3, 4 and 5+ brothers from 2.01 to 3.35, 4.56 and 8.04. If additionally a father was affected the SIRs almost identically increased from 1.89 to 3.48, 4.65 and 8.23. Case numbers decreased almost by a factor of 10 for brothers and of 5 for father-sons by family type. The proportions of affected cases in each family type increased from 15% stepwise to 45%.

We wanted to show detailed family constellation for PCs in 3 generations (**Supplementary Table 2)**. In a large proportion (69.3%) of families a single man was affected, and the proportion of cases from multi-case families declined sharply from 24.6% (2 PCs), 5.1% (3 PCs) and 1.1% (4 or more PCs). However, at the national level case numbers in the multi-case families were not negligible (28,000, 6000 and 1200).

All relative risk (SIR) calculations were done for men in generation 2 (**Supplementary Table 2**). When a man with PC in generation 2 had 1, 2 or more brothers with PC the SIRs increased from 2.00 to 3.33 and successively to 20.02 (6 brothers affected). The proportions of affected cases in the defined family constellations increased from 14.2% (2 brothers with PC) to 72.3% (6 brothers

with PC). Father-son relationships (both with PC) showed SIR of 2.95 between generations 2 and 3, and 1.88 between generations 2 and 1 (with the largest number of cases, N=12,544).

Supplementary Table 2 allows risk assessment in complex family constellations, for example 1 case in each generation, SIR 5.13; 2 or 3 brothers in generation 2 and an affected father and son, SIR 7.00 or 12.77. Generally, any case in generation 3 boosted SIRs because of early onset of these cases; the highest recorded SIR was 41.83 in 3 families with 5 affected brothers and an affected son in generation 3. Conversely, fathers in generation 1 contributed a modest increase in SIR because of their likely high age of onset.

Age-specific familial and cumulative incidence

We wanted to compare incidence rates in second generation depending on the number of affected FDRs in any of the three generations (**Fig. 2A**). The reference (1 case in a family) incidence rate reached a maximum at age 75-79 y; in multi-case families the maxima of the curves shifted step-wise 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 years from 0.15 to 0.6.

Familial risk, metastatic disease and survival

Whether family history (through fathers or brothers) may be associated with metastatic disease, we compared PC patients in generation 2 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 to those lacking family history. The difference was largest in patients diagnosed at age <50 years (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 to the subsequent brothers diagnosed after him (**Fig. 3B**).

High age was a strong predictor of de novo metastases (OR for 80+year old men 3.61) (**Table 2**). In families with up to 2 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; for son of an affected father it was 0.90 and for subsequent brother with an affected father it was 0.60. 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, considering various familial constellations (**Table 3**). Men lacking a family history were the reference group with HR=1.00. In men without de novo metastasis, HR for subsequent brother (whose brother was affected earlier) 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 years), which suggested stronger contribution of family history for subsequent brothers at younger age (HRs 0.74 vs 0.95 in non-metastatic group). Case numbers for metastatic PC we low and the only significant HR of 0.81 (and 0.58 for diagnosis before age 68 years) was for subsequent brother.

DISCUSSION

Family history and blood PSA levels are two important risk factors of PC (14). Here we use a unique three-generation database on 317,000 medically diagnosed PCs from nationally registered family relationships (7). A total of 35,200 PC patients with affected FDRs were included. As comparison, a recent large UK study included 3871 PC patients with affected FDRs (15). The results displayed variation of familial risks (SIRs) among FDRs ranging from 1.88 to 41.8. The first SIR was based on 15,000 father-son pairs between generations 1 and 2; the second SIR was based on 3 families of 5 affected brothers in generation 2 and a patient in each family in generation 3 (**Table 2**). The proportion of affected patients in the whole database was 1 in 10 (9.8%) but the proportion became more unfavorable when more family members were affected, reaching over 50% in many multiplex families. Families where two men were diagnosed with PC accounted 24.6% of affected families, those with 3 PCs accounted for 5.1% and those with 4+ PCs accounted for 1.1%.

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 years. When 2, 3 or 4 family members were diagnosed with PC risk by 80 years 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 (16): *BRCA2* 60%, *BRCA1* 29% and *HOXB13* variant G84E 60% all by age 85 years and *MSH2* 24% by age 75 years. 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 above 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 (17). High risk patients might benefit from early onset and more rigorous follow-up especially in the case of metastatic or advanced prostate cancer in the family (18).

The results offer empirical risk estimates useful for clinical counselling and screening (19). 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 counselling 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 (18, 20-22). Loss of function variants in genes *ATM, BRCA2, MSH2* and *NBN* have been found in aggressive PC (23). However, contribution of social and life-style factors and even overdiagnosis may play a role (13, 24).

Earlier data on mortality in familial PC have been inconsistent as reviewed by Brook et al. (15). 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 awareness of the disease. However, the summary hazard ratio considering the published data was close to 1.00 (15). The present results are in agreement with the Brook et al data with significantly improved survival in familial cases (**Table 3**). We have earlier published survival data showing concordance of both good and poor survival in PC between fathers and sons (25).

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 years (**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 associated with improved survival (**Table 3**).

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 (17). The available schemes usually start with a PSA test and then stratify patients into MRI and/or biopsy groups (26). In Germany, the PROBASE trial is based on early (45 y) PSA determination and resulting risk stratification (27); other modifications have been applied in the ongoing Swedish (Göteborg-2) and Finnish (ProScreen) trials (28, 29). 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 and lacking of detailed characteristics of the tumor (PSA, Gleason and volume, other than T stage), and any treatment. As discussed above, 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, 15).

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 solid basis for clinical risks assessment and management and emphasize further the need to carefully record family history at diagnosis of new cases (19, 30). 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.

FIGURE LEGENDS

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.

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

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

ADDITIONAL INFORMATION

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 to Declaration of Helsinki.

Author contributions
Design: KH, OH
Acquisition of data: KS, JS.
Statistical analysis and interpretation: FZ, KH, AF, AH
Manuscript writing: KH and all other authors.
Approval of the final text: All authors

Conflict of interest
A.H. is shareholder in Circio Holdings ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

Funding
Supported by the SALVAGE project (OP JAK; reg. no. CZ.02.01.01/00/22_008/0004644) - co-financed by the European Union and the state budget of the Czech Republic. the Cooperatio Program, research area SURG, Jane and Aatos Erkko Foundation, Sigrid Juselius Foundation, Finnish Cancer Organizations, University of Helsinki, Helsinki University Central Hospital, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation.

Consent for publication
Own data were used.

References

1. Hemminki K, Sundquist K, Sundquist J, Försti A, Hemminki A, Li X. Familial Risks and Proportions Describing Population Landscape of Familial Cancer. Cancers. 2021;13(17).

2. Vaccarella S, Li M, Bray F, Kvale R, Serraino D, Lorenzoni V, et al. Prostate cancer incidence and mortality in Europe and implications for screening activities: population based study. Bmj. 2024;386:e077738.
3. Zitricky F, Försti A, Hemminki A, Hemminki O, Hemminki K. Conditional Survival in Prostate Cancer in the Nordic Countries Elucidates the Timing of Improvements. Cancers. 2023;15(16).
4. Møller MH, Kristiansen IS, Beisland C, Rørvik J, Støvring H. Trends in stage-specific incidence of prostate cancer in Norway, 1980-2010: a population-based study. BJU Int. 2016;118(4):547-55.
5. Lorenzo Bermejo J, Hemminki K. Familial risk of cancer shortly after diagnosis of the first familial tumor. J Natl Cancer Inst. 2005;97:1575-9.
6. 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.
7. Hemminki K, Ji J, Brandt A, Mousavi SM, Sundquist J. The Swedish Family-Cancer Database 2009: Prospects for histology-specific and immigrant studies. Int J Cancer. 2010;126:2259-67.
8. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age at diagnosis and age at death in familial prostate cancer. Oncologist. 2009;14:1209-17.
9. 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. Eur Urol. 2010;58:275-80.
10. 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. Ann Oncol. 2012(23):i251-6.
11. Xu X, Kharazmi E, Tian Y, Mukama T, Sundquist K, Sundquist J, et al. Risk of prostate cancer in relatives of prostate cancer patients in Sweden: A nationwide cohort study. PLoS Med. 2021;18(6):e1003616.
12. Jansson KF, Akre O, Garmo H, Bill-Axelson A, Adolfsson J, Stattin P, et al. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol. 2012;62(4):656-61.
13. Vickers A, O'Brien F, Montorsi F, Galvin D, Bratt O, Carlsson S, et al. Current policies on early detection of prostate cancer create overdiagnosis and inequity with minimal benefit. Bmj. 2023;381:e071082.
14. Clements MB, Vertosick EA, Guerrios-Rivera L, De Hoedt AM, Hernandez J, Liss MA, et al. Defining the Impact of Family History on Detection of High-grade Prostate Cancer in a Large Multi-institutional Cohort. Eur Urol. 2022;82(2):163-9.
15. Brook MN, H NR, Govindasami K, Dadaev T, Rageevakumar R, Keating D, et al. Family History of Prostate Cancer and Survival Outcomes in the UK Genetic Prostate Cancer Study. Eur Urol. 2023.
16. Finch A, Clark R, Vesprini D, Lorentz J, Kim RH, Thain E, et al. An appraisal of genetic testing for prostate cancer susceptibility. NPJ Precis Oncol. 2022;6(1):43.
17. Van Poppel H, Roobol MJ, Chapple CR, Catto JWF, N'Dow J, Sønksen J, et al. Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021. Eur Urol. 2021;80(6):703-11.
18. Hemminki K, Kiemeney LA, Morgans AK, Ranniko A, Pichler R, Hemminki O, et al. Hereditary and Familial Traits in Urological Cancers and Their Underlying Genes. Eur Urol Open Sci. 2024;69:13-20.

19. Russo J, Giri VN. Germline testing and genetic counselling in prostate cancer. Nature reviews Urology. 2022;19(6):331-43.
20. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016;375(5):443-53.
21. Rantapero T, Wahlfors T, Kähler A, Hultman C, Lindberg J, Tammela TL, et al. Inherited DNA Repair Gene Mutations in Men with Lethal Prostate Cancer. Genes. 2020;11(3).
22. Xu J, Lu J, Gielzak M, Lilly Zheng S, Lu L, Wei J, et al. Germline Testing for Prostate Cancer Patients: Evidence-Based Evaluation of Genes Recommended by NCCN Guidelines. Prostate. 2025;85(12):1087-95.
23. Saunders EJ, Dadaev T, Brook MN, Wakerell S, Govindasami K, Rageevakumar R, et al. Identification of Genes with Rare Loss of Function Variants Associated with Aggressive Prostate Cancer and Survival. European urology oncology. 2024;7(2):248-57.
24. Paschen U, Sturtz S, Fleer D, Lampert U, Skoetz N, Dahm P. Assessment of prostate-specific antigen screening: an evidence-based report by the German Institute for Quality and Efficiency in Health Care. BJU Int. 2022;129(3):280-9.
25. 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.
26. Pinsky PF, Parnes H. Screening for Prostate Cancer. N Engl J Med. 2023;388(15):1405-14.
27. Krilaviciute A, Albers P, Lakes J, Radtke JP, Herkommer K, Gschwend J, et al. Adherence to a risk-adapted screening strategy for prostate cancer: First results of the PROBASE trial. Int J Cancer. 2023;152(5):854-64.
28. Auvinen A, Tammela TLJ, Mirtti T, Lilja H, Tolonen T, Kenttämies A, et al. Prostate Cancer Screening With PSA, Kallikrein Panel, and MRI: The ProScreen Randomized Trial. Jama. 2024;331(17):1452-9.
29. Möller F, Månsson M, Wallström J, Hellström M, Hugosson J, Arnsrud Godtman R. Prostate Cancers in the Prostate-specific Antigen Interval of 1.8-3 ng/ml: Results from the Göteborg-2 Prostate Cancer Screening Trial. Eur Urol. 2024;86(2):95-100.
30. Hemminki K, Eng C. Clinical genetic counselling for familial cancers requires reliable data on familial cancer risks and general action plans. J Med Genet. 2004;41:801-7.

Table 1. SIR for PC in second generation based (listed on first column) on number of family members affected with PC in two generations.

Family members with PC by generation						
2nd	**1st**	**N at risk**	**N familal**	**Proportion affected (%)[1)]**	**SIR**	**[95% CI]**
2	0	73481	12720	17.3	2.01	[1.98-2.05]
3	0	6870	1858	27.0	3.35	[3.2-3.51]
4	0	842	287	34.1	4.56	[4.05-5.12]
5+	0	199	89	44.7	8.04	[6.46-9.9]
1	1	106562	15087	14.2	1.89	[1.86-1.92]
2	1	14030	3662	26.1	3.48	[3.37-3.6]
3	1	1806	592	32.8	4.65	[4.29-5.05]
4+	1	349	173	49.6	8.23	[7.05-9.56]
	Total	204139	34468	16.9		

[1)] Proportion affected: % of N affected of N at risk.

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 model with logit link function).

	N (N_{events})	OR	[95% CI]
Age group			
50-59	17564 (576}	1	ref.
<50	1447 (52)	1.16	[0.87 - 1.54]
60-69	55568 (2320)	1.29	[1.18 - 1.42]
70-79	39552 (2347)	2.07	[1.88 - 2.28]
80+	5107 (436)	3.61	[3.15 - 4.13]
Family history			
Non-familial	86263 (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	16844 (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	119238 (5731)	0.96	[0.95 - 0.96]

Table 3 Cox proportional hazards model to assess influence of family history on overall survival in non-metastatic (M0, including Mx) and metastatic (M1) patients, in all ages and by age groups (young/old, split at median diagnostic age). Hazard ratios (HR) adjusted for age and calendar year. HRs significantly different from 1 are bolded.

Family member with PC	**M0 all ages**			**M0 age<67**			**M0 age>=67**			**M1 all ages**			**M1 age<67**			**M1 age>=67**		
	N (N events)	HR	[95% CI]	N (N events)	HR	[95% CI]	N (N events)	HR	[95% CI]	N (N events)	HR	[95% CI]	N (N events)	HR	[95% CI]	N (N events)	HR	[95% CI]
Non-familial	78856 (12398)	1	ref.	34702 (3384)	1	ref.	44154 (9014)	1	ref.	4213 (2865)	1	ref.	1447 (1006)	1	ref.	2766 (1859)	1	ref.
First brother	5043 (898)	0.95	[0.89 - 1.02]	2739 (324)	0.93	[0.83 - 1.04]	2304 (574)	0.97	[0.89 - 1.05]	301 (226)	0.93	[0.81 - 1.07]	150 (112)	0.87	[0.72 - 1.06]	151 (114)	0.99	[0.82 - 1.20]
Second brother	6464 (896)	**0.90**	**[0.84 - 0.96]**	2271 (168)	**0.74**	**[0.64 - 0.87]**	4193 (728)	0.95	[0.88 - 1.02]	252 (144)	**0.81**	**[0.68 - 0.95]**	37 (15)	**0.58**	**[0.35 - 0.97]**	215 (129)	0.86	[0.72 - 1.02]
Son of father with PC	15526 (1733)	**0.88**	**[0.84 - 0.93]**	9180 (615)	**0.81**	**[0.74 - 0.88]**	6346 (1118)	**0.92**	**[0.86 - 0.98]**	668 (425)	0.99	[0.90 - 1.10]	313 (203)	0.98	[0.84 - 1.14]	355 (222)	0.99	[0.86 - 1.14]
First brother and father with PC	1526 (193)	**0.81**	**[0.70 - 0.94]**	1028 (96)	**0.82**	**[0.66 - 0.99]**	498 (97)	**0.80**	**[0.65 -0.98]**	65 (52)	1.15	[0.87 - 1.51]	34 (26)	1.03	[0.70 -1.52]	31 (26)	1.28	[0.87 - 1.88]
Second brother and father with PC	1880 (178)	**0.75**	**[0.65 - 0.87]**	919 (54)	**0.72**	**[0.55 - 0.94]**	961 (124)	**0.77**	**[0.64 - 0.92]**	54 (27)	0.74	[0.50 - 1.07]	12 (5)	0.44	[0.18 - 1.06]	42 (22)	0.89	[0.58 - 1.35]

Fig. 1

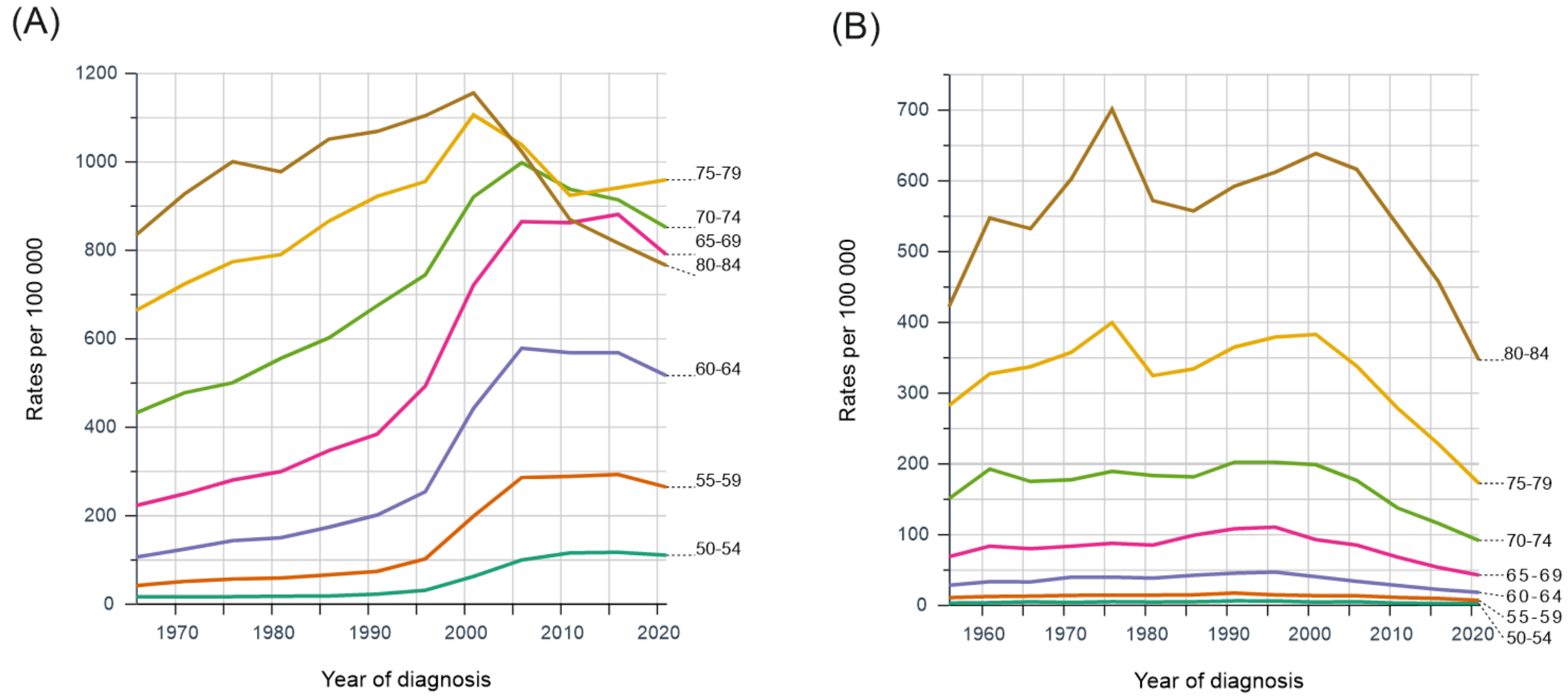

(A)
Rates per 100 000
1200
1000
800
600
400
200
0
1970
1980
1990
2000
2010
2020
Year of diagnosis
75-79
70-74
65-69
80-84
60-64
55-59
50-54
(B)
Rates per 100 000
700
600
500
400
300
200
100
0
1960
1970
1980
1990
2000
2010
2020
Year of diagnosis
80-84
75-79
70-74
65-69
60-64
55-59
50-54

Fig. 2

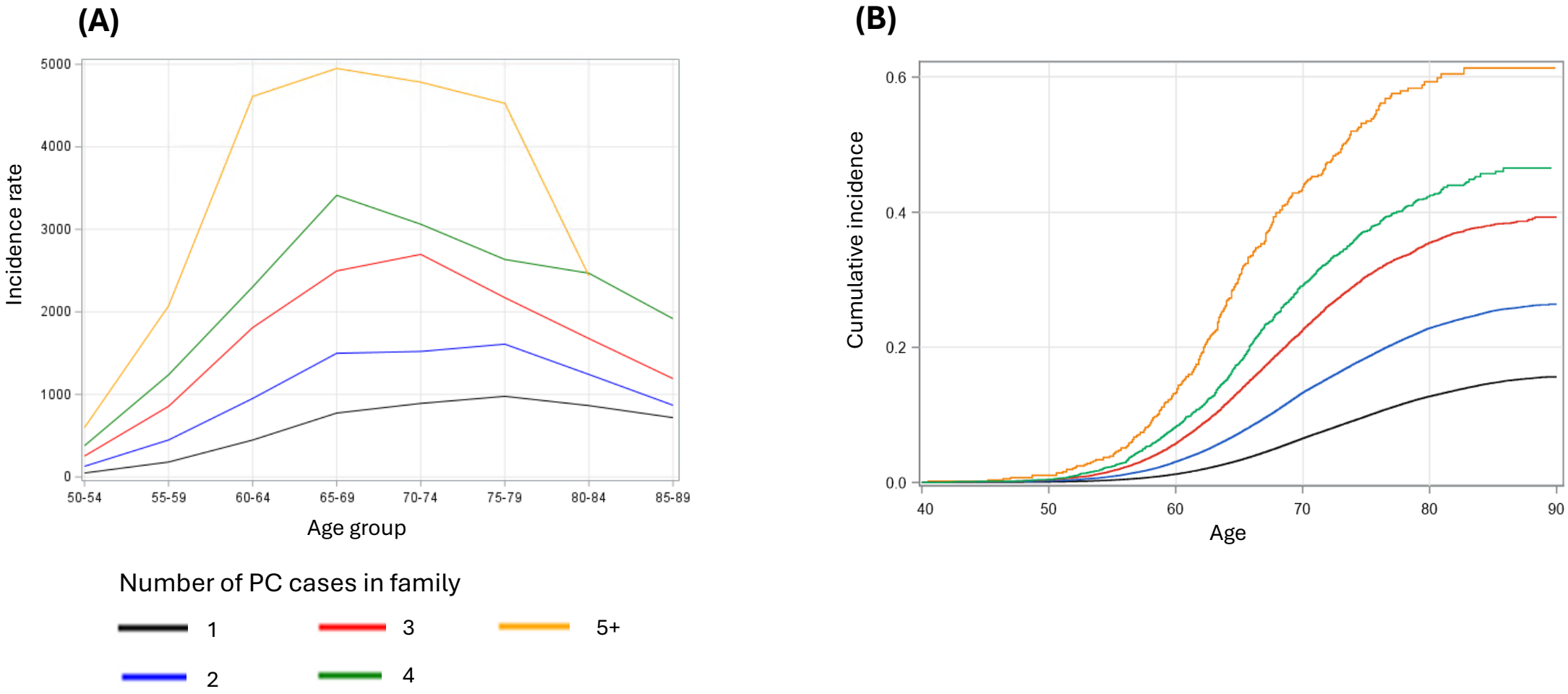
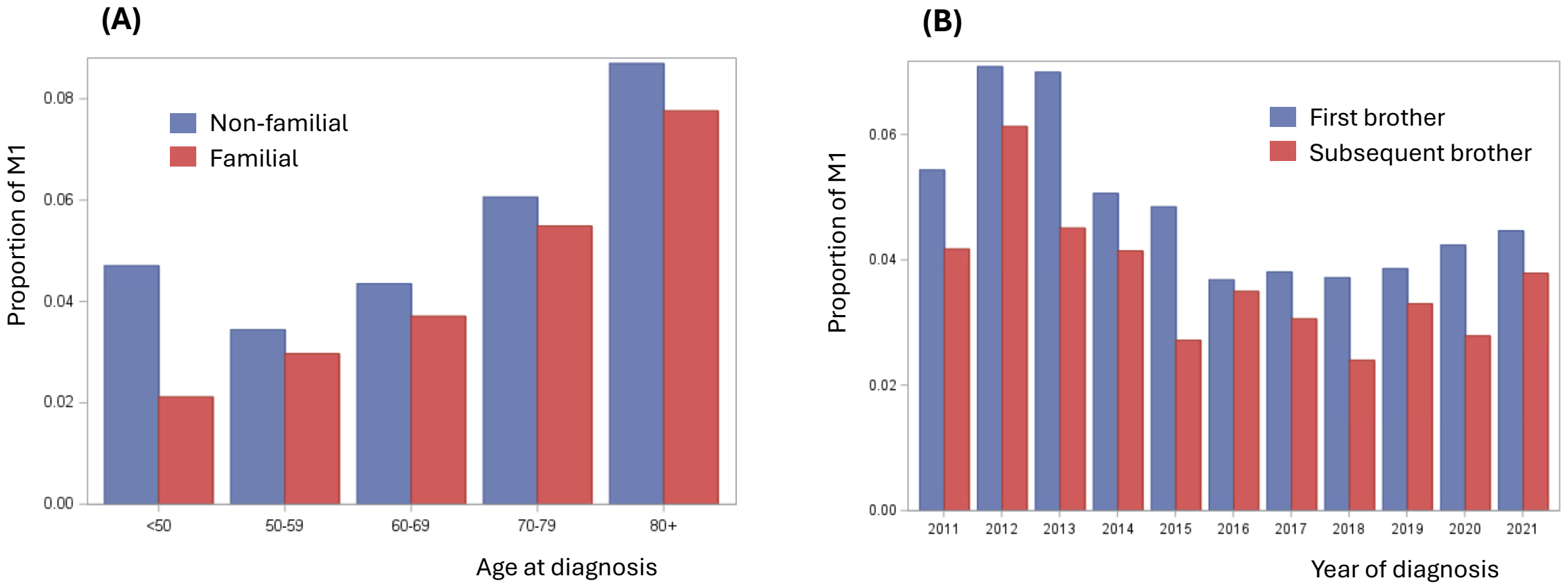

(A)
Incidence rate
5000
4000
3000
2000
1000
0
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
Age group
Number of PC cases in family
1
2
3
4
5+
(B)
Cumulative incidence
0.6
0.4
0.2
0.0
40
50
60
70
80
90
Age

Fig. 3


(A)
Proportion of M1
0.08
0.06
0.04
0.02
0.00
Non-familial
Familial
<50
50-59
60-69
70-79
80+
Age at diagnosis
(B)
Proportion of M1
0.06
0.04
0.02
0.00
First brother
Subsequent brother
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year of diagnosis

SUPPLEMENT

Supplementary Methods

Swedish incidence and mortality trends were shown from the earliest available data until 2021 using the NORDCAN database through International Agency for Cancer web site on Global Cancer Observatory (see https://nordcan.iarc.fr/). The rates were age-standardized.

For purpose of relative risk calculation, we consider generation 1 born before 1932 (median birth year 1912), generation 2 born in Sweden from 1932 onwards (median birth year 1947) and generation 3 children of parents from generation 2 (median birth year 1976). The population structure is presented in **Supplementary Table 1**. Numbers of males, all their cancers and PCs were dominated by generation 1. Of 316,471 PCs close to 60% were diagnosed in generation 1, slightly less than their share of all cancers (63%). The age group with most diagnosed PCs was 10 years higher in generation 1 (75-79 y) compared to generation 2. In generation 1, PC accounted for 30% of all male cancers, while in generation 2 the share of PC was 40%.

All family and cancer linkages were done through the unique personal identification number.

Relative risks were calculated for generation 2 (born in Sweden with both identified parents) using first degree relatives (FDRs, fathers, brothers, sons) as probands. Using generation 2 was selected as it covered essentially all age groups.

Incidence rates by family history were calculated in 5-year age-brackets for incident cases in a defined age-group divided by person-years at risk in the same age-group. Cases were the sets of brothers who were diagnosed with PC.

Cumulative incidence of PC by family history was calculated for men at risk at 40 years of age, using CIF macro in SAS. The competing risk was death and follow-up was censored at date of emigration or end of study (29th December 2021).

The analyses of metastic status and survival included all cases with available familial links (born since 1932). The modelling of probability of metastasis and Cox models were run on subset on patients with maximum one brother with PC (2 brothers per family).

Supplementary Table 1. Overview of the studied Swedish male population divided in three generations.

Generation	Year of birth median [min max]	Total males	Cancer cases in males	PC cases	Age group with most PC cases	Paternal history of PC proportion
1st	1912 [1865 1931]	1 985 583	616 478	188 767	75-79	
2nd	1947 [1932 1978]	1 178 087	297 903	119 965	65-69	17 %
3rd	1976 [1946 2021]	1 524 360	48 723	7 917	55-59	

Supplementary Table 2. SIR for PC in second generation based (listed on first column) on number of family members affected with PC in three generation.

Family members with PC by generation							
2nd	**1st**	**3nd**	**N affected**	**N at risk**	**Proportion affected (%)[1)]**	**SIR**	**[95% CI]**
1	0	0	79705	964816	8.3	1	(ref.)
1	0	1	857	2759	31.1	2.96	[2.77-3.17]
1	0	2	38	85	44.7	5.33	[3.77-7.32]
1	0	3	2	2	100	17.7	[2.14-63.92]
1	1	0	14888	105727	14.1	1.88	[1.85-1.91]
1	1	1	188	406	46.3	5.13	[4.42-5.92]
1	1	2	11	14	78.6	11.98	[5.98-21.44]
2	0	0	12544	72757	17.2	2.00	[1.96-2.03]
2	0	1	174	390	44.6	4.91	[4.21-5.7]
2	0	2	2	7	28.6	2.51	[0.3-9.08]
2	1	0	3607	13858	26	3.45	[3.34-3.57]
2	1	1	52	95	54.7	7.00	[5.23-9.18]
3	0	0	1833	6775	27.1	3.33	[3.18-3.48]
3	0	1	22	51	43.1	5.65	[3.54-8.55]
3	0	2	3	3	100	19.79	[4.08-57.82]
3	1	0	580	1773	32.7	4.59	[4.23-4.98]
3	1	1	12	15	80	12.77	[6.6-22.3]
4	0	0	279	821	34	4.48	[3.97-5.04]
4	0	1	8	10	80	12.38	[5.35-24.4]
4	1	0	118	257	45.9	7.41	[6.14-8.88]
5	0	0	51	134	38.1	5.99	[4.46-7.88]
5	0	1	3	3	100	41.83	[8.63-122]
5	1	0	30	50	60	8.15	[5.5-11.63]
6	0	0	34	47	72.3	20.02	[13.9-27.98]
6	1	0	18	24	75	22.84	[13.54-36.1]
7	1	0	7	11	63.6	15.46	[6.22-31.86]
	Total		115066	1170890	9.8 %		

1) Proportion affected: % of N affected of N at risk.