Risk of Invasive Prostate Cancer and Prostate Cancer Death in Relatives of Patients With Prostatic Borderline or In Situ Neoplasia: A Nationwide Cohort Study

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BACKGROUND: The question of whether having a family history of prostatic borderline or in situ neoplasia (PBISN) is associated with an increased risk of invasive prostate cancer (PCa) or death from PCa remains unanswered. The objective of the current study was to provide an evidence-based risk estimation for the relatives of patients with PBISN. METHODS: Nationwide Swedish family cancer data sets were used for the current study, including data regarding all residents of Sweden who were born after 1931 and their parents. Standardized incidence ratios (SIRs), standardized mortality ratios (SMRs), and lifetime cumulative risks of PCa were calculated for men with different constellations of family history. Family history was defined as a dynamic (time-dependent) variable considering changes during follow-up (1958-2015). RESULTS: Of the 6,343,727 men in the current study, a total of 238,961 developed invasive PCa and 5756 were diagnosed with PBISN during the follow-up. Men with 1 first-degree relative who was diagnosed with PBISN had a 70% increased risk of invasive PCa (SIR, 1.7; 95% confidence interval, 1.5-1.9) and PBISN death (SMR, 1.7; 95% confidence interval, 1.3-2.2) compared with men with no family history of PBISN or invasive PCs. These were rather close to estimates in men with 1 first-degree relative diagnosed with invasive PCa (SIR, 2.1 and SMR, 1.8). A higher risk of PCa in family members was found among patients with a family history of PBISN and/or PCa diagnosed before age 60 years. The results in terms of cumulative risk resembled this trend. CONCLUSIONS: A family history of PBISN appears to be as important as a family history of invasive PCa with regard to an increased risk of invasive PCa or PCa mortality. Such a history should not be overlooked in PCa screening recommendations or in future research regarding familial PCa. Cancer 2020;126:4371-4378. © 2020 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: familial risk, family history, prostate cancer, prostate carcinoma in situ, prostatic borderline neoplasia, prostatic in situ neoplasia, screening.

INTRODUCTION
Prostate cancer (PCa) is the second most common cancer among men, the fifth leading cause of cancer death in the world, and the leading cause of cancer death in 46 countries.1 However, despite the high prevalence and mortality of PCa, to our knowledge its causes have remained poorly understood.

Family history has been proposed by various studies to be the strongest risk factor for PCa. Previous studies have reported that having a brother or father with PCa is associated with a doubled risk of developing this cancer.2-4 Men with a family history of invasive PCa already have been undergoing screening earlier than the general population.5-8 The majority of invasive cancers arise from carcinomas in situ. They are considered to be preinvasive (premalignancy) lesions due to their potential to become cancerous and spread to other nearby locations.9-12 Several types of prostatic borderline or in situ neoplasia (PBISN) that are found during prostate biopsy have been proposed to be precancerous lesions, including...

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prostatic intraepithelial neoplasia, atypical small acinar proliferation, and proliferative inflammatory atrophy.\textsuperscript{13,14} As a result of developments in screening techniques and clinical diagnostic methods, carcinomas in situ are becoming more commonly diagnosed.\textsuperscript{15} To our knowledge, it remains unclear whether having a family history of PBISN is associated with an increased risk of invasive PCa or death due to PCa in other family members. Because a family history of invasive PCa is the strongest known risk factor for invasive PCa, the role of a family history of PBISN in this regard is worth investigating.

Using what to our knowledge is the world’s largest nationwide, register-based genealogy information and high-quality cancer registry data from Sweden, the current study investigated the association between family history of PBISN and the risk of invasive PCa, taking the dynamic nature of family history into account.

MATERIALS AND METHODS

Participants
The Swedish family cancer data sets were linked, combining information from the Swedish Population Register and national censuses, the Swedish Cancer Register, and the Swedish Cause of Death Register. Data regarding family relationships were obtained from the Swedish Multi-generation Register, in which children born in Sweden after 1931 are registered along with their parents as families. In this nationwide cohort study, the age of the offspring generation (individuals born after 1931) was limited to 85 years, but the age of the parents was not limited. This register was linked by the individually unique national registration number to the Swedish Cancer Register data from 1958 to 2015. A 4-digit diagnostic code according to the seventh revision of the International Classification of Diseases (ICD-7) and subsequent ICD classifications was available. The behavior of prostate tumors (borderline, in situ, or invasive) was defined using the Swedish Cancer Register based on the third digit of the pathological anatomic diagnosis code from 1958 to 1992 and the fifth digit of the morphology code in International Classification of Diseases for Oncology, Second Edition (ICD-O-2) or ICD-O-3 from 1993 onward (1, 2, or 3, respectively).

An additional linkage was performed to the national census data up to 1990 to obtain data regarding socioeconomic background (blue collar worker, white collar worker, farmer, private, professional, or other and/or unspecified) and residential area. After 1990, data regarding annual family income and residential area were obtained using the Swedish Population Register. The underlying cause of death was available from the Swedish Cause of Death Register. The 2015 version of the research data sets (updated in 2017) included \( > 12.8 \) million individuals (6,343,727 men) with genealogical data, and approximately 1.7 million primary invasive tumors (859,391 men) and \( > 500,000 \) borderline or in situ tumors (119,063 men). All residents of Sweden born after 1931 and their parents were included with the exception of 1,530,395 men who had no registered first-degree relatives (FDRs) in the data sets. More details regarding the data sets used in the current study have been reported elsewhere.\textsuperscript{16}

Statistical Analyses
Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated to compare the relative risks of PCa and death from PCa for individuals with a history of PBISN or invasive PCa in their FDRs with the risks in their counterparts without such a history. The follow-up started at birth, immigration, or the starting date of the study (January 1, 1958), whichever came latest. It ended at the year of PCa diagnosis, year of emigration, year of death, or the closing date of the study (December 31, 2015), whichever came earliest. Family histories presented in the current study were exclusive. For example, having one FDR affected with PBISN indicates that other FDRs did not have PBISN or invasive PCa and second-degree relatives also did not have PBISN or invasive PCa. A definition of a dynamic family history was used, namely establishing the family history of every participant at the time of entry into the study, changing the family history every time a new family member was diagnosed as having invasive PCa or PBISN, and disregarding changes in family history occurring after the time that the participant was diagnosed with invasive PCa or died. The dynamic (time-varying or time-dependent) method of family history assessment has been explained in detail elsewhere.\textsuperscript{17} A schematic figure showing the dynamic method is presented in the Supporting Information (see Supporting Fig. 1). For example, assume the father of an index man was diagnosed with PBISN in 1969, his older brother was diagnosed with PCa in 1980, he himself was diagnosed with PCa in 2000, and his younger brother was diagnosed with PCa in 2009. In the dynamic method, during the period between 1969 and 1979, the index man would be considered with a family history of only 1 FDR with PBISN, whereas in the static method, the same man in the same period would be considered to have 2 FDRs with invasive PCa and 1 FDR with PBISN (in fact, for
the entire study period, 1958-2015, even if the cancer in the younger brother was diagnosed after the diagnosis of PCA in himself or his own death.

SIRs (and SMRs) were calculated as the ratio of the observed to the expected number of incident PCA cases (or deaths from PCA). All relative risk estimates in the current study (SIRs and SMRs) were adjusted for age (5-year bands), calendar period (5-year bands), socioeconomic status (blue collar worker, white collar worker, farmer, private, professional, or other and/or unspecified), and residential area (large cities, other cities in south Sweden or north Sweden, or unspecified). In addition, we adjusted our relative risk estimates for hospitalization for chronic obstructive pulmonary disease (COPD, as a surrogate for heavy smoking), obesity, and alcoholism. The expected numbers were calculated from the strata-specific cancer incidence and/or mortality rate in those in the population with no family history of a prostate tumor multiplied by the corresponding person-years for subjects with a specific family history of prostate tumor (eg, one brother). The 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution. Sensitivity analysis was performed to compare the results of risk estimation for different periods (ie, before and after 1990) and subtypes of prostatic neoplasia (ie, prostatic borderline neoplasia and prostatic in situ neoplasia). An additional analysis was performed by excluding cases of PBISN that later became invasive. The cutoff value for age at diagnosis was set at 60 years. The cutoff value for age at death due to PCA was set at 70 years due to the rarity of death before age 60 years in general in Sweden, with only 2 cases with a family history of PBISN who died before age 60 years reported. However, additional analyses by a cutoff age for death of 60 years were conducted.

Cumulative risk up to 80 years (which approximates lifetime risk, given a life expectancy of 80 years for Swedish men in 2015) was calculated based on the following equations: age-specific annual incidence rate = number of cases for each 1-year age divided by person-years for that age; lifetime cumulative rate = sum of all age-specific incidence rates by age 79 years; and lifetime cumulative risk = 1 − exp (− lifetime cumulative rate).

Exact values for person-years from individual data (not from conventional aggregated data) were used in the calculation of cumulative incidences. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina). The personal identifiers were pseudonymized (ie, were replaced with technical serial numbers) to prevent the identification of individuals in the database.

The study protocol was approved by the Lund Regional Ethics Committee (ref 2012/795).

RESULTS

Among the study population of 6,343,727 men, a total of 238,196 men (3.8%) were diagnosed with primary invasive PCA and 5756 men (0.09%) were diagnosed with PBISN. Of those with PBISN, 3272 men (56.8%) were classified as having borderline neoplasia and 2484 (43.2%) as having in situ neoplasia. During up to 58 years of follow-up (1958-2015), a total of 70,197 men (29.5% of the patients with PCA) died of PCA. In total, 1165 patients with PCA first were diagnosed with PBISN and that later was found to have developed into invasive PCA during follow-up, accounting for 17% of patients with PBISN.

Risk of Invasive PCA

Relative risk

Having 1 FDR diagnosed with PBISN was associated with a 70% increased risk of invasive PCA (SIR, 1.7; 95% CI, 1.5-1.9) compared with men with no family history of PBISN or invasive PCA (Table 1). The risk of invasive PCA in those with 1 FDR diagnosed with invasive PCA was approximately 2-fold (95% CI, 2.1-fold to 2.1-fold). Further relative risk estimates by detailed type of relationship are presented in Supporting Table 1. As an example, in men with an affected father with PBISN, the risk of invasive PCA was found to be increased by approximately 80% (SIR, 1.8; 95% CI, 1.5-2.0) and by approximately 70% in men with an affected brother (SIR, 1.7; 95% CI, 1.3-2.0).

A higher relative risk of invasive PCA in family members was found in patients whose relatives received a diagnosis of PBISN at earlier ages, especially in patients diagnosed at age <60 years (Table 1). For example, the risk of invasive PCA before age 60 years in men with 1 FDR diagnosed with PBISN before age 60 years was 3.1-fold higher than the risk in their counterparts in the general population without any family history of PBISN or invasive PCA, whereas this risk was 1.6 in those affected at age ≥60 years and had an FDR diagnosed at age ≥60 years.

Cumulative risk

The results by cumulative risk also were in keeping with those of relative risk (Table 2). The cumulative risk of being diagnosed with PCA by age 50 years in a man with 1 FDR diagnosed with PBISN was 0.2%, the same as that for men with a family history of invasive PCA. The lifetime risk (by age 79 years) of developing PCA in a man with
FDR With PBISN

FDR With Invasive PCa

Years was 2.0-fold higher than the risk in his counterparts in the population without any family history of PBISN or invasive PCa.

We also compared the results by separating PBISN into periods adjusted by period at diagnosis. The analysis demonstrated consistent results (see Supporting Tables 4-6).

Sensitivity Analysis

We performed a sensitivity analysis by calendar period at the time of diagnosis comparing our results for the period at or before 1990 with the results from the entire period adjusted by period at diagnosis. The analysis demonstrated consistent results (see Supporting Tables 4-6). We also compared the results by separating PBISN into prostatic borderline neoplasia and prostatic in situ neoplasia and found no significant difference with regard to risk estimates between these 2 subtypes (see Supporting Tables 7-9). Further adjustment for hospitalization for COPD, obesity, and alcoholism did not appear to change the results substantially (data not shown).

In an additional analysis, after excluding men with a family history of PBISN that later became invasive, the results of the current study did not change substantially (see Supporting Tables 10 and 11). For example, having 1 FDR diagnosed with PBISN still was associated with a 1.7-fold increased risk of invasive PCa (SIR, 1.7; 95% CI, 1.5-1.9) and a 1.6-fold increased risk of death from PCa (SMR, 1.6; 95% CI, 1.1-2.1).

### DISCUSSION

Using what to the best of our knowledge is the world's largest nationwide linked data sets concerning cancer status and genealogical information with up to 58 years of follow-up, we found that having 1 FDR diagnosed with PBISN was associated with increased risks of developing invasive PCa and dying of PCa, on a magnitude close to that of having a FDR affected with invasive PCa. We also observed a higher familial risk of invasive PCa in men whose relatives received a diagnosis of PBISN at earlier ages compared with those whose relatives were diagnosed with PBISN at older ages. The importance of a family history of invasive PCa has been well recognized, and earlier screening for relatives of patients with invasive PCa has been recommended by current guidelines. For example, the American Cancer Society recommendations for the early detection of prostate cancer advise that men who have an FDR diagnosed with PCa before age 65 years should initiate screening 5 years earlier than average-risk men in the general population. The similarity between

| Age at Diagnosis, Years | Index Man Relative | No. | SIR | 95% CI | No. | SIR | 95% CI | No. | SIR | 95% CI | No. | SIR | 95% CI |
|------------------------|-------------------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|
| All                    | All               | 269 | 1.7 | 1.5-1.9 | 18,205 | 2.1 | 2.1-2.1 | 44 | 2.6 | 1.9-3.4 | 1818 | 4.2 | 4.0-4.4 |
| <60                    | 37                | 2.0 | 1.4-2.7 | 1964 | 2.9 | 2.7-3.0 | 15 | 2.7 | 1.5-4.3 | 694 | 5.1 | 4.7-5.5 |
| ≥60                    | 232               | 1.7 | 1.5-1.9 | 16,241 | 2.0 | 2.0-2.1 | 29 | 2.5 | 1.7-3.6 | 1124 | 3.8 | 3.6-4.1 |
| All                    | 46                | 2.1 | 1.6-2.8 | 4117 | 3.0 | 2.9-3.0 | 2 | 1.7 | 0.2-5.6 | 326 | 11 | 9.7-12 |
| <60                    | 7                 | 3.1 | 1.3-6.2 | 481 | 5.2 | 4.7-5.6 | 1 | 1.8 | 0.0-8.4 | 226 | 13 | 11-15 |
| ≥60                    | 39                | 2.0 | 1.4-2.7 | 3636 | 2.8 | 2.7-2.9 | 1 | 1.7 | 0.0-7.9 | 100 | 8.0 | 6.5-9.7 |
| ≥60                    | 30                | 1.9 | 1.3-2.6 | 1483 | 2.5 | 2.4-2.6 | 14 | 2.8 | 1.5-4.6 | 468 | 3.9 | 3.8-4.3 |
| ≥60                    | 193               | 1.6 | 1.4-1.8 | 12,605 | 1.9 | 1.9-1.9 | 28 | 2.6 | 1.7-3.7 | 1024 | 3.7 | 3.4-3.9 |

Abbreviations: 95% CI, 95% confidence interval; FDR, first-degree relative; PBISN, prostatic borderline or in situ neoplasia; PCa, prostate cancer; SIR, standardized incidence ratio.

Bold value indicates significant (95% CI did not include unity).

*Example: The risk of developing early-onset invasive PCa (before age 60 years) for a man with a family history of PBISN in 1 of his FDRs diagnosed at age ≥60 years was 2.0-fold higher than the risk in his counterparts in the population without any family history of PBISN or invasive PCa.

| Age at Diagnosis, Years | Index Man Relative | No. | SIR | 95% CI | No. | SIR | 95% CI | No. | SIR | 95% CI | No. | SIR | 95% CI |
|------------------------|-------------------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|
| All                    | All               | 269 | 1.7 | 1.5-1.9 | 18,205 | 2.1 | 2.1-2.1 | 44 | 2.6 | 1.9-3.4 | 1818 | 4.2 | 4.0-4.4 |
| <60                    | 37                | 2.0 | 1.4-2.7 | 1964 | 2.9 | 2.7-3.0 | 15 | 2.7 | 1.5-4.3 | 694 | 5.1 | 4.7-5.5 |
| ≥60                    | 232               | 1.7 | 1.5-1.9 | 16,241 | 2.0 | 2.0-2.1 | 29 | 2.5 | 1.7-3.6 | 1124 | 3.8 | 3.6-4.1 |
| All                    | 46                | 2.1 | 1.6-2.8 | 4117 | 3.0 | 2.9-3.0 | 2 | 1.7 | 0.2-5.6 | 326 | 11 | 9.7-12 |
| <60                    | 7                 | 3.1 | 1.3-6.2 | 481 | 5.2 | 4.7-5.6 | 1 | 1.8 | 0.0-8.4 | 226 | 13 | 11-15 |
| ≥60                    | 39                | 2.0 | 1.4-2.7 | 3636 | 2.8 | 2.7-2.9 | 1 | 1.7 | 0.0-7.9 | 100 | 8.0 | 6.5-9.7 |
| ≥60                    | 30                | 1.9 | 1.3-2.6 | 1483 | 2.5 | 2.4-2.6 | 14 | 2.8 | 1.5-4.6 | 468 | 3.9 | 3.8-4.3 |
| ≥60                    | 193               | 1.6 | 1.4-1.8 | 12,605 | 1.9 | 1.9-1.9 | 28 | 2.6 | 1.7-3.7 | 1024 | 3.7 | 3.4-3.9 |
TABLE 2. Cumulative Risk of Invasive PCa in Men With a Family History of PBISN or Invasive PCa by Age

| Patient With PCa in Family | Cumulative Risk in Index Man by Age, Years | Lifetime Risk
|---------------------------|-------------------------------------------|----------------|
|                           | Birth to 39 Years | Birth to 44 Years | Birth to 49 Years | Birth to 54 Years | Birth to 59 Years | Birth to 64 Years | Birth to 69 Years | Birth to 74 Years | Birth to 79 Years | 95% CI | No. |
| No family history of PBISN or invasive PCa | 0.0 | 0.0 | 0.0 | 0.2 | 0.7 | 2.1 | 4.5 | 8.0 | 12 | 12-12 | 174,152 |
| 1 FDR with PBISN | 0.0 | 0.0 | 0.2 | 0.9 | 2.5 | 6.6 | 13a | 18 | 24a | 21-27 | 257 |
| 1 FDR with invasive PCa | 0.0 | 0.0 | 0.2 | 1.1 | 3.5 | 8.3 | 15 | 22 | 28 | 27-28 | 17,785 |
| 1 FDR with PBISN and 1 FDR with invasive PCa | 0.0 | 0.0 | 4.3 | 4.3 | 5.0 | 15 | 23 | 32 | 32 | 22-41 | 43 |
| 2 FDRs with invasive PCa | 0.0 | 1.1 | 3.6 | 8.4 | 17 | 28 | 38 | 46 | 52 | 50-54 | 1799 |

Abbreviations: 95% CI, 95% confidence interval; FDR, first-degree relative; PBISN, prostatic borderline or in situ neoplasia; PCa, prostate cancer.

Example: The cumulative risk of developing PCa by age 69 years in a man with 1 FDR with PBISN was 13% compared with the 4.5% risk in his counterparts in the general population without any affected FDR. The lifetime risk (by age 79 years) for that man was 24%, whereas the lifetime risk in men without any affected FDR was 12%.

TABLE 3. SMR of Death Due to Invasive PCa in Men With a Family History of PBISN or Invasive PCa by Age at Death in Index Man (Cutoff Age of 70 Years)a and Age at PCa Diagnosis in Relatives (Cutoff Age of 60 Years)

| Age at Death, Years | Age at Diagnosis, Years | 1 FDR With PBISN | 1 FDR With Invasive PCa | 1 FDR With Invasive PCa and 1 FDR With PBISN | 2 FDRs With Invasive PCa |
|---------------------|------------------------|------------------|------------------------|---------------------------------------------|-------------------------|
| Index Man Relative  | No. | SMR | 95% CI | No. | SMR | 95% CI | No. | SMR | 95% CI | No. | SMR | 95% CI |
| All All <60 | 42 | 1.7 | 1.2-2.2 | 2077 | 1.8 | 1.7-1.9 | 10 | 3.7 | 1.8-6.6 | 192 | 2.6 | 2.4-3.2 |
| ≥60 | 30 | 1.6 | 1.1-2.3 | 1604 | 1.7 | 1.6-1.8 | 7 | 3.8 | 1.5-7.5 | 121 | 2.6 | 2.1-3.1 |
| <70 All <60 | 15 | 2.1 | 1.2-3.4 | 783 | 1.8 | 1.7-2.0 | 4 | 5.9 | 1.6-14 | 65 | 3.5 | 2.7-4.5 |
| ≥60 | 3 | 4.4 | 0.9-12 | 82 | 2.8 | 2.3-3.5 | 2 | 8.2 | 1.0-26 | 27 | 3.9 | 2.6-5.6 |
| ≥70 All <60 | 12 | 1.8 | 1.0-3.1 | 701 | 1.8b | 1.6-1.9 | 2 | 4.6 | 0.6-15 | 38 | 3.3 | 2.3-4.5 |
| ≥60 | 27 | 1.5 | 1.0-2.2 | 1294 | 1.8 | 1.7-1.9 | 6 | 3.0 | 1.1-6.1 | 127 | 2.6 | 2.1-3.0 |
| <70 All <60 | 9 | 1.5 | 0.7-2.8 | 391 | 2.4 | 2.2-2.6 | 1 | 1.6 | 0.0-7.5 | 44 | 3.1 | 2.2-4.1 |
| ≥60 | 18 | 1.5 | 0.9-2.3 | 903 | 1.6 | 1.5-1.7 | 5 | 3.6 | 1.2-7.8 | 83 | 2.3 | 1.9-2.9 |

Abbreviations: 95% CI, 95% confidence interval; FDR, first-degree relative; PBISN, prostatic borderline or in situ neoplasia; PCa, prostate cancer; SMR, standardized mortality ratio.

Bold value indicates significant (95% CI did not include unity).

See also Supporting Table 3 for cutoff age of 60 years in the index individuals.

Example: The risk of dying of PCa before age 70 years in a man with a family history of invasive PCa in 1 of his FDRs was 1.8-fold higher than the risk in his counterparts in the population without any family history of PBISN or invasive PCa.
a family history of PBISN and that of invasive PCAs with regard to an increased risk of invasive PCa or death due to PCa as reported in the current study suggests that for an informed screening decision in the future, a family history of PBISN could be taken into account and given equal weight. The findings of the current study have suggested expanding the definition of a high-risk population to include those with a family history of PBISN for consideration in clinical counselling for the early detection of PCa.

A family history of invasive PCa is known to be the strongest risk factor for invasive PCa. However, to our knowledge, the question of whether having a family history of PBISN also is associated with an increased risk of invasive PCa has not been studied before. Increased risks of invasive melanoma and cancers of the colon, breast, and cervix have been observed in the presence of concordant (similar site) carcinoma in situ or invasive cancers in family members. To the best of our knowledge, the current study is the first to demonstrate the significant association between a family history of PBISN and an increased risk of invasive PCa. We reported the relative and absolute risks of being diagnosed with invasive PCa with regard to having a family history of PBISN considering age at the time of diagnosis of the prostate tumor in patients and their relatives. The importance of age at the time of diagnosis of invasive PCa in relatives on the familial risk of invasive PCa already has been reported. The results of the current study demonstrated that this finding also applies to PBISN in relatives. We demonstrated that having 1 FDR diagnosed with PBISN was associated with a 1.7-fold increased risk of invasive PCa compared with men with no family history of PBISN or invasive PCa, which was close to the 2-fold increased risk observed in those with 1 FDR diagnosed with invasive PCa. Similar results after the exclusion of patients with PBISN that later became invasive may suggest that the familial risk associated with a family history of PBISN is in itself important, even without progression into invasive PCa.

Men with a family history of invasive PCa have been reported to be at an increased risk of dying of PCa. We observed that men with 1 FDR diagnosed with PBISN also were at an increased risk of dying of PCa, similar to men with a history of invasive PCa in 1 FDR. This finding demonstrated that the scope of risk associated with a family history of PBISN is not limited to developing PCa, but extends to death due to PCa, which is a more definitive outcome.

To the best of our knowledge, there already are several types of noninvasive cellular proliferations in the prostate gland that are deemed to be clinically significant. When high-grade prostatic intraepithelial neoplasia is found on core needle biopsy, there is an approximately 50% risk of detecting carcinoma on subsequent biopsies over 3 years. The closeness of the impact of a family history of PBISN and invasive PCa strengthens the evidence of their likely biological similarity. The results of the current study have suggested that the diagnosis of PBISN also is important for the relatives of such patients.

We used what to our knowledge are the largest family cancer data sets in the world to investigate the association between family history of PBISN and the risk of invasive PCa in a comprehensive way, which resulted in novel evidence-based, clinically relevant information. The similarity of results using invasive PCa as the primary outcome and those with death due to PCa as a confirmatory secondary outcome ensured that the current study findings did not primarily reflect the overdiagnosis of (indolent) PCa due to more screening taking place among family members of patients with prostate tumors. Another important advantage of the current study was the accuracy and completeness of the analyzed data sets, thereby mitigating biases related to overreporting and underreporting of family history as well as selection and recall biases, because we used register-based family history (not patient self-reports), medically verified cancer status, and precise timing of the diagnosis of PBISN and invasive PCa in index men and their relatives from long-standing, high-quality, nationwide registry data. The Swedish Cancer Registry and Swedish Cause of Death Register were reported to be of high completeness and accuracy. A Swedish study also found little or no bias in the overall estimates of familial risk of PCa in the Swedish Multi-generation Register. Regional differences in risk estimates most likely were reconciled by our adjustment for area of residence.

In addition to the traditional prostate-specific antigen test, other techniques such as ultrasonography, multiparametric magnetic resonance imaging, and computed tomography now are available for the detection and diagnosis of PCa, which results in more men receiving a diagnosis of PBISN. Based on the current study findings, in a real-world scenario, the awareness for the family members of patients with PBISN should start from the time of diagnosis of PBISN and possible action not be postponed until the diagnosis of invasive PCa in family members. One of the strengths of the current study was the use of the dynamic definition of a family history of PBISN and invasive PCa, which not only took into account the dynamic nature of a family history of PCa every time a
new family member was diagnosed, but also dealt with the transition from PBISN to invasive PCa and avoided the reverse association (PBISN in an affected relative had been diagnosed before diagnosis of the invasive PCa in the index man, not after it). Similarly, for men with multiple affected FDRs, the dynamic nature of the age of the youngest diagnosed relative was considered, allowing for variation throughout the follow-up period whenever a subsequent affected FDR was diagnosed at a younger age.

It has been suggested that overdiagnosis caused by overscreening among men with a family history might inflate the familial risk. However, our sensitivity analysis for the period after the introduction of the prostate-specific antigen test in Sweden (1990s) demonstrated results that were consistent with the whole period, suggesting a low likelihood of influence by overscreening. In addition, analyses by Brandt et al have suggested that familial aggregation of PCa is not due to screening habits shared within a family, a speculated scenario in which a close relative of a patient with cancer may take part in screening more often and earlier than the rest of the population. Considering the high familial risks present in fatal PCa, family history remains an important source of information that is useful for clinical genetic counselling, and it has been suggested that initiating screening before the diagnosis of any PCa within a family does not appear to be warranted.

A limitation of the current study was that, in our database, no data were available regarding other risk factors for PCa (eg, race and/or ethnicity). In general, to our knowledge, very few well-established strong risk factors have been identified for PCa. Apart from age, 2 other established risk factors are race and/or ethnicity and family history. Compared with the 2-fold increase in risk associated with having 1 affected FDR, the lifetime risk of being diagnosed with PCa for African American men is only increased by 1.4-fold. It has been reported before that the increased familial risk of PCa does not vary by ethnicity. We had no detailed data available regarding race, smoking history, alcohol consumption, physical activity, adiposity, diet, or medication use, which also may potentially play roles in the development of PCa. Even though the relationship between risk of PCa and lifestyle factors such as diet and smoking remain a matter of debate (not to mention their role as confounders for familial risk of PCa, which was the focus of the current study), all relative risk estimates (SIRs and SMRs) in the current study were adjusted for age, calendar period, socioeconomic status, and residential area to mitigate the potential but not established influence of lifestyle factors. Further adjustment for hospitalization for COPD, obesity, and alcoholism did not substantially change the current study results. To our knowledge, limited data were available regarding precise familial risks based on large-scale cohort studies from outside of Sweden. However, based on similarities found for invasive cancers, we believe that the current study estimates for familial risks of PBISN are likely to be generalizable to populations with approximately similar PCa incidence and mortality patterns.

The results of the current study have provided novel evidence-based information for clinicians and for the relatives of men who have been diagnosed with PBISN. Having a family history of PBISN was found to be associated with an increased risk of invasive PCa and death from PCa on a magnitude close to that for having a family history of invasive PCa. This clinically relevant finding, especially the increased risk of death from PCa in those patients with a family history of PBISN, deserves careful consideration in risk-adapted PCa counseling and early detection strategies and could supplement current PCa screening guidelines.

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**CONFLICT OF INTEREST DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

Xing Xu, Mahdi Fallah, and Elham Kharazmi analyzed the data, interpreted the results, and drafted the article. Mahdi Fallah and Elham Kharazmi conceptualized and designed the study. Kristina Sundquist and Jan Sundquist provided the study material. All authors reviewed the article for important intellectual content and approved the final version.

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