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## Original Paper

# Familial and Hereditary Prostate Cancer in Southern Sweden. A Population-based Case–Control Study

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**The objectives of this study were to investigate the effect of family history on prostate cancer risk, to estimate the incidence of hereditary prostate cancer in southern Sweden and to assess the reliability of self-reported family history of prostate cancer. The study included consecutive prostate cancer patients and age-matched control subjects from a geographically defined population. The controls consisted of 1 male patient with malignant melanoma or non-Hodgkin's lymphoma and 1 male from the community per prostate cancer case. Family history was assessed with questionnaires, and diagnoses of fathers and brothers of cases were validated by the Southern Swedish Regional Tumour Registry. Among fathers and brothers whose names and birth dates were available, 56 (92%) of the 61 reported prostate cancer diagnoses were verified. Fifteen per cent of 356 cases and 5.0% of 712 controls reported at least 1 case of prostate cancer among their brothers or fathers, giving a relative risk of 3.2 (95% confidence interval 2.1–5.1). The relative risk increased with decreasing age at diagnosis of the patient. Based on the pedigree, 3.1% of the 356 patients were classified as having hereditary prostate cancer. This proportion was significantly higher among patients diagnosed before the age of 60 years (7.1%) than among older patients (2.2%). We conclude that there is a substantially increased risk of prostate cancer for sons and brothers of prostate cancer patients. The risk increases with decreasing age at diagnosis of the patient as an effect of a higher prevalence of hereditary prostate among early onset cases. Furthermore, we found self-reported family history of prostate cancer to be a valid estimate of the true incidence of prostate cancer in fathers and brothers of men with prostate cancer.** © **1999 Elsevier Science Ltd. All rights reserved.**

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## INTRODUCTION

FAMILY HISTORY as a risk factor for prostate cancer was first reported by Woolf in 1960 [1]. During the last decade a large number of confirmatory studies have been published [2–18], and family history is now the best characterised risk factor for prostate cancer together with age and race [19]. Previous epidemiological studies have indicated that sons and brothers of men with prostate cancer have a 2–3-fold increase in the risk of developing prostate cancer. The population-based cohort studies have yielded the lowest estimates of relative risk [2–4], whereas the results of case–control studies have been more varied with generally higher risks [5–18]. A contributory cause of the different results from cohort studies as compared with case–control studies could be that self-reported family history is an unreliable measure of the incidence of prostate cancer in relatives. In two of the case–control studies a minority of the diagnoses of the relatives were validated [6, 13], whereas no validation at all was reported in the other studies.

In the early 1990s the existence of a hereditary form of prostate cancer was recognised as an explanation for the frequent familial clustering of the disease [20]. A segregation analysis based on patients with clinically localised prostate cancer indicated that approximately 9% of the total number of prostate cancer cases, and as much as 43% of cases

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diagnosed before the age of 55 years, were caused by an autosomally inherited susceptibility to the disease [20]. A genome-wide search with linkage analysis led, in 1996, to the localisation of a highly penetrant gene to the long arm of chromosome 1, conferring a susceptibility for prostate cancer in approximately one-third of the families with clinical evidence of hereditary prostate cancer [21]. This gene, which has as yet not been identified, was named *HPC1* (hereditary prostate cancer gene 1). Since no associated gene has been identified, hereditary prostate cancer is presently defined only by the number of prostate cancer cases in the pedigree. The generally accepted definition includes nuclear families with 3 cases of prostate cancer, occurrence of prostate cancer in each of three generations in the paternal or maternal lineage, and a cluster of two relatives diagnosed with prostate cancer before the age of 55 years [22]. American researchers have reported that approximately 5% of prostate cancer patients can be classified as hereditary prostate cancer cases based on their family history [13, 22], but none of these studies were population-based.

The aims of the present case–control study were to estimate the effect of family history on prostate cancer risk and the incidence of hereditary prostate cancer in a geographically defined population in southern Sweden. Since the accuracy of family history data is crucial for the results of case–control studies, we also assessed the reliability of self-reported family history of prostate cancer by means of cancer registry validation of diagnoses.

## MATERIALS AND METHODS

*Cases*

All prostate cancer patients diagnosed in the Lund and Helsingborg healthcare districts (470 000 inhabitants in total) during 1995 and 1996 were identified through the Southern Swedish Regional Tumour Registry. A total of 531 cases were diagnosed during this time period. A questionnaire with questions about name, birth date, history of cancer in first- and second-degree relatives, anthropometric data and various potential environmental risk factors were handed to the prostate cancer patients by their urologists 3–9 months after diagnosis. The following cases were excluded: 40 patients who died before or just after receiving the questionnaire; 39 patients who were judged too ill (physically or mentally) to participate; 31 patients with accidentally diagnosed cancer (stage T1a); 10 patients who were adopted or immigrants; 5 patients not fully informed of their diagnosis; and 3 patients who emigrated. Of the remaining 403 patients, 356 (88%) returned the questionnaire with satisfactory data concerning their first-degree relatives. Accordingly, information was collected from 71% of all diagnosed clinical cases (T1a cases excluded). The median age at diagnosis of all 531 diagnosed cases was 73.7 years (range 44–94 years), compared with 72.1 years (range 44–94 years) for those returning the questionnaire. Of the 356 responders, 247 reported at least one brother, 237 of whom had at least one brother aged 50 years or more. The total number of brothers was 513.

Only 31 of the 356 patients were diagnosed before the age of 60 years. To improve the power of the study in this early onset group, we included patients diagnosed before the age of 60 years between January 1995 and September 1997 from the rest of the Southern healthcare region (total 1.5 million inhabitants). These latter patients returned 82 questionnaires which were used only when calculating relative risks for patients before the age of 60 years. The response rate for patients younger than 60 years was 97% in the Lund and Helsingborg districts and 70% in the Southern healthcare region. Of the total 113 responders aged 60 years or less, 77 reported at least one brother, 62 of whom had at least one brother aged 50 years or more.

Information on second-degree relatives was usually incomplete and was therefore not used when calculating relative risks. However, since we also aimed to estimate the incidence of hereditary prostate cancer, cases reporting a positive family history of prostate cancer who did not report adequate data for second-degree relatives were contacted by telephone and asked to supplement information about second- and third-degree relatives.

*Control groups*

Two different control groups were used. One group consisted of male patients with malignant melanoma ($n = 214$ ) or non-Hodgkin's lymphoma ($n = 142$) diagnosed in the Southern healthcare region between 1991 and 1996, who shortly after the time of diagnosis were sent a questionnaire similar to the one used for the prostate cancer patients. The only differences were that name and birth dates of relatives were not included, and that questions about environmental factors were somewhat different. The response rate for these cancer patients was 81%. From the responders were randomly selected one control per case, matched to the prostate cancer cases for age at diagnosis in 5-year categories. Of these 356 cancer controls, 256 reported at least one brother. The total number of brothers was 551.

The second control group consisted of randomly chosen men among residents in southern Sweden, originally matched for year of birth to the melanoma and non-Hodgkin's lymphoma patients. These men were sent questionnaires identical to those sent to the melanoma and non-Hodgkin's lymphoma patients. The response rate was 67%. As for the other control group, one age-matched control per prostate cancer case was randomly selected from the responders. Of these 356 population controls, 261 reported at least one brother. The total number of brothers was 572.

*Statistics*

Relative risks of prostate cancer with confidence intervals (CI) were calculated using conditional logistic regression. The incidence of prostate cancer was similar in the two control groups and they were, therefore, analysed together as one control group. Since validation of diagnoses was possible only for cases and not for controls, the statistical analysis was based on the number of relatives of cases initially reported as being diagnosed with prostate cancer and not on those relatives actually identified as prostate cancer cases by the cancer registry. CI for the proportions of patients with hereditary prostate cancer were calculated using statistics for the binomial distribution. Significance levels for differences between these proportions were calculated with Fisher's exact test. All *P* values were two-tailed.

## RESULTS

*Reliability of self-reported family history of prostate cancer*

The cancer incidence for fathers and brothers of cases whose names and birth dates were available was established by the Southern Swedish Regional Tumour Registry. Such validation of diagnoses was possible for 61 of the 79 fathers

*Table* 1. *Family history of prostate cancer among* 356 *cases with recently diagnosed prostate cancer and* 712 *age-matched controls in a population-based study from southern Sweden*

| Affected family member | No. (%) of cases ($n = 356$) | No. (%) of cancer controls* ($n = 356$) | No. (%) of population controls ($n = 356$) | RR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Father and/or brother | 54 (15.2%) | 18 (5.0%) | 18 (5.0%) | 3.2 | 2.1–5.1 | < 0.0001 |
| Father only | 24 (7%) | 11 (3.1%) | 12 (3.4%) | 2.2 | 1.2–4.0 | 0.008 |
| One brother only | 23 (6%) | 7 (2.0%) | 6 (1.7%) | 3.6 | 1.8–7.2 | 0.0003 |

*Patients with malignant melanoma or non-Hodgkin's lymphoma diagnosed in southern Sweden between 1991 and 1996. RR, relative risk; CI, confidence interval.

and brothers reported to have prostate cancer. 56 of these 61 (92%) were identified by the cancer registry as prostate cancer cases, whereas the remaining 5 turned out to have bladder cancer (2), rectal cancer (2) or were not found in the register (1). Conversely, 7 cases of prostate cancer were found in fathers and brothers not reported to have prostate cancer. These were instead reported as having 'prostatic disease' (3), 'cancer' (3) or 'skeletal cancer' (1). Thus, when including the false positives, the number of relatives with prostate cancer reported by the patients ($n = 61$) was 97% of the total number of relatives identified as prostate cancer cases ($n = 63$) by the cancer registry.

*Familial prostate cancer*

54 (15%) of the 356 patients from the Lund and Helsingborg districts reported at least one brother or a father diagnosed with prostate cancer. No sons were reported as having prostate cancer. 1 patient reported prostate cancer in two brothers, and 6 patients reported that both their father and one brother were affected. The median age at diagnosis of patients with a family history of prostate cancer was 71.7 years compared with 72.3 years for sporadic cases. The median age at diagnosis of relatives reported with prostate cancer was 70.0 years.

Familial prostate cancer was more prevalent among the 113 patients diagnosed at the age of 60 years or less, of whom 24 (21%) reported a father or brother with prostate cancer.

The number of cases and controls reporting a family history of prostate cancer with calculated relative risks, including the effect of age and of whether a brother or a father was affected, are shown in Tables 1 and 2.

*Hereditary prostate cancer*

The generally accepted definition of hereditary prostate cancer includes nuclear families with three cases of prostate cancer, occurrence of prostate cancer in each of three generations in the paternal or maternal lineage of the proband and a cluster of two relatives diagnosed with prostate cancer before the age of 55 years [22]. A family history consistent with these clinical criteria was reported by 11 of the 356 cases from Lund and Helsingborg (3.1%, 95% CI 1.6–5.5%) and by 9 of the 237 patients reporting at least one brother aged 50 years or more (3.8%, 95% CI 1.8–7.1%). The median age at diagnosis was 65.4 years for these 11 cases and 68.0 years for the 44 relatives with prostate cancer in the 15 families with hereditary prostate cancer identified in the study. The proportion of patients classified as having hereditary prostate cancer was 7.1% (8/113; 95% CI 3.1–13.5%) among those diagnosed before the age of 60 years compared with only 2.2% (7/324; 95% CI 0.9–4.4%) among those diagnosed later in life ($P = 0.03$). For patients reporting at least one brother aged 50 years or more, the corresponding figures were 13% (8/62; 95% CI 5.7–24%) and 2.3% (5/218; 95% CI 0.7–5.2%, $P < 0.001$). None of the 712 controls reported prostate cancer in more than one relative. In eight of the 11 families from Lund and Helsingborg the father of the proband was affected, whereas three families showed evidence of maternal inheritance to the proband, although in two of these paternal inheritance was found in other parts of the pedigree. 7 of the 8 cases with hereditary prostate cancer diagnosed before the age of 60 years had a father with prostate cancer. In one of the expanded pedigrees, 8 verified and 1 probable case of prostate cancer were found in five nuclear families in three generations (Figure 1). The members of this family spread over a large geographical area at the beginning of the century, making common environmental risk factors highly unlikely as the cause of the aggregation of prostate cancer in this family.

## DISCUSSION

This case–control study was based on consecutive patients with recently diagnosed prostate cancer from a geographically defined population in southern Sweden. Family history was validated by the regional tumour registry, which verified 92% of the prostate cancer diagnoses reported for relatives of cases. In accordance with previous case–control studies [5–18] we found a highly significant increased relative risk (3.2) of prostate cancer for men with a family history of prostate

*Table* 2. *The effect of age at diagnosis on relative risk of prostate cancer*

| Age of proband at diagnosis | Father and/or brother RR (95% CI) | Father affected RR (95% CI) | One brother affected RR (95% CI) |
|---|---|---|---|
| < 60 years (113* cases, 226 controls) | 5.1 (2.4–10) | 3.1 (1.4–6.7) | † |
| 60–75 years (196 cases, 392 controls) | 3.2 (1.7–5.9) | 2.1 (0.9–4.9) | 3.6 (1.4–9.4) |
| > 75 years (129 cases, 258 controls) | 2.3 (1.1–4.7) | 1.7 (0.6–4.2) | 2.8 (0.9–8.2) |

*Including 31 patients from the Lund and Helsingborg districts and 82 patients from the rest of the Southern healthcare region. †None of the 226 controls aged < 60 years reported a brother with prostate cancer making it impossible to calculate the relative risk. 9 (8%) of the 113 cases reported one brother diagnosed with prostate cancer. RR, relative risk; CI, confidence interval.

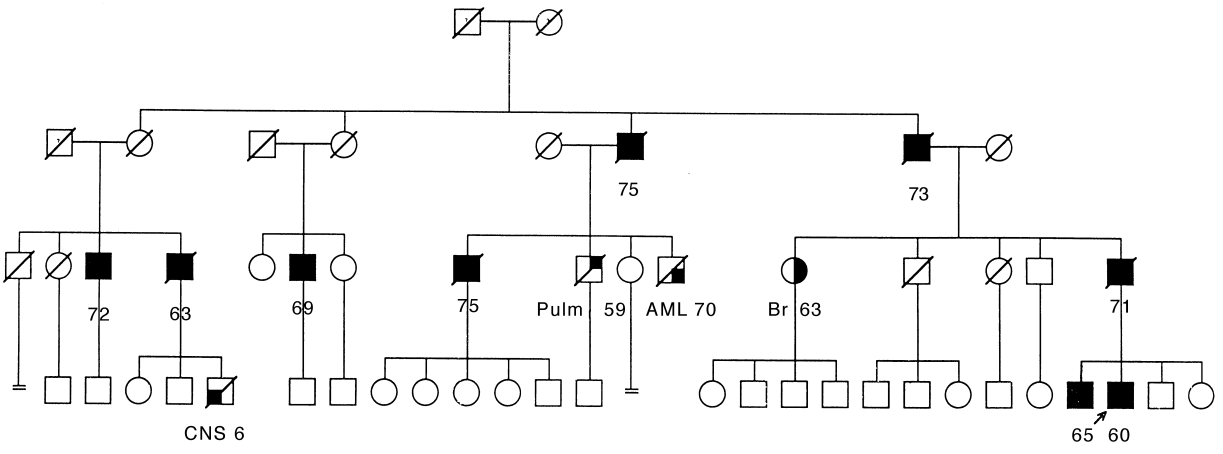


**Figure 1. Pedigree of a family with hereditary prostate cancer. Black squares represent men diagnosed with prostate cancer and partially filled squares and circles represent men and women diagnosed with other types of cancer. Figures refer to the age at diagnosis of cancer. The arrow indicates the proband, 1 of the cases in the present case–control study. Pulm, pulmonary; AMC, acute myeloid leukaemia; Br, breast; CNS, central nervous system.**

cancer. As in other studies the risk increase was more pronounced for relatives of patients diagnosed at an early age, with a relative risk of 5.1 in relatives of cases diagnosed before the age of 60 years. The risk was somewhat larger for brothers than for fathers, a finding that has also been made in most previous case–control studies [8–17] and has evoked the hypothesis that susceptibility for prostate cancer might be transmitted by X-linked or recessive inheritance in some families [12].

The incidence of hereditary prostate cancer has not previously been reported from a population-based study. Of the 356 newly diagnosed prostate cancer cases from Lund and Helsingborg, 3.1% had hereditary prostate cancer according to the clinical definition of the syndrome [22]. The proportion of hereditary prostate cancer was significantly higher among patients diagnosed before the age of 60 years (7.1%) than among older patients (2.2%). Hereditary prostate cancer was somewhat less common in our study than previously reported from two American centres (5.1% [20] and 5.6% [13]). However, the American studies were not population-based and the patients in those studies were younger. Furthermore, the widespread screening for prostate cancer in the U.S.A. may be a source of bias, since men with a family history of prostate cancer are more interested in participation in screening programmes [23].

As long as hereditary prostate cancer is defined by pedigree only, rather than by the results of genetic analyses, estimates of the frequency of hereditary prostate cancer will be very approximate. Most likely the proportion of patients with families fitting the clinical definition of hereditary prostate cancer is significantly lower than the true proportion of prostate cancer patients with an inherited susceptibility as the major cause of their disease. Few patients in the present study were classified as hereditary cases based on a pedigree with maternal inheritance, which demonstrates the difficulties in using pedigree for the identification of an autosomally inherited disease in which the phenotype is expressed in one sex only. The hereditary nature of prostate cancers caused by maternally transmitted mutations in *HPC1* or other autosomally dominant genes is difficult to recognise unless the patients have many brothers. For early onset cases this difficulty is even more pronounced since their brothers are likely to be young and, therefore, less likely to be diagnosed with prostate cancer, even if they are carriers of a mutated prostate cancer susceptibility gene. Naturally, defining hereditary prostate cancer by pedigree will also include false positive cases when a cluster of prostate cancer in a family is actually caused by shared environmental factors or is just due to chance. However, false positive families are less likely to occur than false negative ones. In view of these considerations, the results of our study indicate that the true proportion of hereditary prostate cancer in southern Sweden is in the range of 5–10% of the total number of prostate cancer cases, which is in accordance with estimates from the U.S.A. [22].

In agreement with other case–control studies, we found that the relative risk of prostate cancer in brothers and sons of patients with prostate cancer increased with decreasing age of the patient. This corresponded with a significantly higher prevalence of hereditary prostate cancer among patients diagnosed before the age of 60 years (7.1%) than among older patients (2.2%). The hereditary prostate cancer cases in the present study were diagnosed on average 7 years earlier than were the sporadic cases. Likewise, the median age at diagnosis of the 44 relatives with hereditary prostate cancer was 7 years below the median age at diagnosis of prostate cancer in the population (the median age at diagnosis in southern Sweden has been fairly constant around 75 years during the last 40 years). These figures are in perfect agreement with the results from studies from the U.S.A. [24] and support the hypothesis that clusters of early onset prostate cancer in families are mostly caused by an inherited susceptibility for prostate cancer. Considering the likelihood of false negative families discussed above, we estimate the frequency of hereditary prostate cancer in patients diagnosed before the age of 60 years in southern Sweden to be approximately 20–35%. This estimate relies on the assumption that hereditary prostate cancer is mainly caused by autosomally dominant susceptibility genes with high penetrance. However, there may very well be multiple prostate cancer genes with different patterns of inheritance and variable penetrance. In the original report, the *HPC1* locus on chromosome 1q was linked to one-third of the analysed families [21], but since two of four later studies [25–28] failed to confirm linkage to the locus on

1q24-25 the true proportion might be lower. If a significant proportion of hereditary prostate cancer cases is in fact caused by rather common, but lowly penetrant genes, it will be difficult to identify the involved genes and, therefore, also difficult to define the total proportion of hereditary prostate cancer.

To our knowledge, the diagnoses of relatives of prostate cancer patients in a case–control study have not previously been as extensively validated as in the present study. Names and birth dates were available for most of the fathers and brothers of cases, which permitted validation of the reported prostate cancer diagnoses by the regional cancer registry. When summarising the effects of false positive and false negative prostate cancer diagnoses, the reported number of relatives with prostate cancer was 97% of the number of prostate cancer diagnoses identified by the cancer registry. The accuracy of a family history of prostate cancer was higher in our study than in previous studies of the reliability of self-reported family history of cancer [29–31], which could be explained by cultural differences.

Validation of diagnoses could only be performed for relatives of the prostate cancer cases, but not for relatives of the controls. Most likely, the cancer diagnoses of relatives in the control group are the weak link in all case–control studies regarding family history of prostate cancer. We found no difference in family history of prostate cancer between the cancer control group (patients diagnosed with malignant melanoma or non-Hodgkin's lymphoma) and the population control group. This similarity between the two control groups indicates that recall bias, i.e. that a cancer patient is more likely to recall cancer in relatives than people without cancer, was not essential in this study. A more likely source of bias is that many men with prostate cancer do not disclose their diagnosis to their relatives. Prostate cancer is a disease which may cause no or only mild symptoms for several years and is commonly treated conservatively. Prostate cancer is, therefore, easier than many other cancers to conceal from relatives. Many of the patients in this study were contacted by telephone to supplement their family history, and several of them mentioned that they had been unaware that a brother had prostate cancer until they told their families about their disease. Such information bias leads to an overestimation of relative risks in case–control studies, and may partly explain why these have in general yielded higher relative risks than population-based cohort studies.

A third type of bias to be considered is detection bias. Male relatives of prostate cancer patients are concerned about possible inheritance [32] and are, therefore, more likely to have a prostatic examination in the absence of significant symptoms from the urinary tract. Detection bias could be especially relevant for brothers of recently diagnosed prostate cancer patients, which may contribute to the more pronounced increase in risk if a brother rather than a father had prostate cancer in this and other case–control studies of prostate cancer.

As regards selection bias, this study benefits from its population-based design and from the high response rate (88% of patients in the Lund and Helsingborg districts). If one assumed that all non-responders had a negative family history, the point estimate of relative risk would only decrease from 3.2 to 2.8. The response rate for patients diagnosed before the age of 60 years was substantially lower (70%). This was probably an effect of the fact that this age group included patients from a larger geographical area and that most of these patients received the questionnaire by mail instead of from their urologist. However, the response rate in this early onset group was very high among patients from the Lund and Helsingborg districts (97%), and since the proportion of patients with a positive family history was similar for the 31 patients from Lund and Helsingborg (8/31 = 26%) as for the 82 patients from the rest of the region (16/82 = 20%), selection bias is unlikely to be the cause of the higher relative risk for relatives of early onset cases.

In conclusion, self-reported family history of prostate cancer is a valid estimate of the true incidence of prostate cancer in fathers and brothers of men with prostate cancer. There is a substantially increased risk of prostate cancer for sons and brothers of prostate cancer patients, which increases with decreasing age at diagnosis of the patient. Familial aggregation of prostate cancer is, in many cases, caused by an autosomal dominantly inherited susceptibility to prostate cancer. The syndrome of hereditary prostate cancer is significantly more prevalent among patients diagnosed before the age of 60 years than among older patients. These findings make it logical to consider screening for men who have a brother or a father diagnosed with prostate cancer before the age of 60 years and for those who have more than one relative with prostate cancer. The high incidence of prostate cancer in this selected group of men, together with the early age at onset of hereditary prostate cancer, will affect the cost–benefit balance of screening in a positive way compared with screening the general population.


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