HEREDITARY ASPECTS OF PROSTATE CANCER

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Abstract • Résumé

Objective: To review current literature on the hereditary aspects of prostate cancer and to evaluate the importance of family history in history taking and screening for prostate cancer.

Data sources: MEDLINE was searched for articles in English or French published between Jan. 1, 1956, and Oct. 31, 1994, with the use of MeSH headings "prostatic neoplasms," "genetics" and "chromosomes." Additional references were selected from the bibliographies of articles found during the search.

Study selection: Case–control studies involving the incidence of prostate cancer and relative risk (RR) of such cancer in the families of men with this disease, compared with a control group, were included. Only studies in which prostate cancer was diagnosed on the basis of histologic tests were included. Animal investigations were excluded.

Data extraction: Ten case–control studies were evaluated critically in terms of design, case and control groups, the size of the samples and statistical results. The incidence of prostate cancer in the families of cases, compared with that in the families of controls, and differences in RR were reviewed.

Data synthesis: The lifetime risk of prostate cancer is 9.5% and of death from prostate cancer is 2.9% for a man 50 years of age. For first-degree male relatives of men with prostate cancer, the calculated RR ranges from 1.7 to 8.73. "Hereditary" prostate cancer is a term applied to a specific subset of patients with prostate cancer. This form of prostate cancer is transmitted by a rare, autosomal, dominant allele with high penetrance; it accounts for an estimated 43% of early-onset disease (affecting men less than 55 years of age) but only 9% of all prostate cancer in men up to 85 years of age. A greater number of affected family members and early onset among family members are the most significant predictors of risk.

Conclusions: Recent confirmation of the familial clustering and Mendelian inheritance patterns of some prostate cancer has important implications. It increases the potential for directed research into the causes of prostate cancer and for refinements in the current screening practices to detect this common disease. Manoeuvres to detect prostate cancer should be started earlier among men with one or more first-degree relatives with the disease than among other men.

Objectif : Examiner des publications courantes sur les aspects héréditaires du cancer de la prostate et évaluer l'importance des antécédents familiaux dans l'établissement du dossier médical et le dépistage du cancer de la prostate.

Sources de données : On a effectué dans MEDLINE une recherche d'articles publiés en anglais ou en français entre le 1er janvier 1956 et le 31 octobre 1994 en utilisant les en-têtes de sujets matières médicaux MeSH «prostatic neoplasms», «genetics» et «chromosomes.» On a choisi d'autres références dans les bibliographies d'articles trouvés au cours de la recherche.

Sélection d'études : Les études cas–témoins portant sur l'incidence du cancer de la prostate et le risque relatif (RR) du cancer en question dans les familles d'hommes atteints de cette maladie, comparativement à un groupe témoin, ont été incluses. Seules les études où l'on a diagnostiqué un cancer de la prostate à la suite de tests histologiques ont été incluses. Les études sur les animaux ont été exclues.

Extraction de données : Dix études cas–témoins ont été soumises à un examen critique qui a porté sur la conception, les cas et les groupes témoins, la taille des échantillons et les résultats statistiques. On a examiné l'incidence du cancer de la prostate dans les familles de cas, comparativement à celle qui a été établie dans les familles de sujets témoins, et les écarts au niveau du RR.

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Synthèse des données : Pour un homme de 50 ans, le risque à vie de cancer de la prostate est de 9,5 % et celui de mort des suites d'un cancer de la prostate s'établit à 2,9 %. Dans le cas des parents masculins du premier degré d'hommes atteints du cancer de la prostate, le RR calculé varie de 1,7 % à 8,73 %. L'expression cancer «héréditaire» de la prostate est appliquée à un sous-ensemble précis de patients atteints d'un cancer de la prostate. Cette forme de cancer de la prostate est transmise par un allèle dominant autosomique rare à pénétrance élevée et représente un pourcentage estimatif de 43 % des cas de maladie à apparition précoce (chez les hommes de moins de 55 ans), mais 9 % seulement du total des cas de cancer de la prostate chez les hommes de 85 ans et moins. Un nombre plus élevé de membres de la famille qui sont atteints et l'apparition précoce chez des membres de la famille sont les prédicteurs les plus significatifs du risque.

Conclusion : La confirmation récente du grappage familial et des tendances héréditaires mendéliennes de certains cancers de la prostate a d'importantes répercussions. Elle accroît la possibilité de recherches dirigées sur les causes du cancer de la prostate et de raffinement des techniques actuelles de dépistage de cette maladie répandue. Les manoeuvres de dépistage du cancer de la prostate devraient commencer plus tôt dans le cas des hommes qui ont un ou plusieurs parents du premier degré atteints de la maladie que chez les autres hommes.

Cancer of the prostate is the most common type of cancer and the second most common cause of death from cancer in Canadian men.[1] An estimated 16 100 men will be diagnosed with prostate cancer and 4200 men will die from this disease in 1995. Prostate cancer is expected to account for 12.0% of all deaths from cancer among men this year. The lifetime risk of prostate cancer is 9.5% and of dying of the disease 2.9% for a man 50 years of age.[2] Since 1970 the incidence and mortality rates have been increasing.[1]

Numerous studies have attempted to elucidate the factors associated with prostate cancer. The following have been implicated: geography,[3–5] occupation,[3,5] fertility,[3,4,6] sexual activity and infectious agents,[4–8] ethnic background,[3–5] education levels,[4] diet,[3–5] sex-hormone levels[4,5] and familial characteristics.

The observation that certain families are susceptible to cancer is not new. In 1895 Warthin used the term "cancer family" to refer to families with excessive numbers of a single type or multiple types of neoplasms.[9] This high incidence of cancer in a certain family could be due to a combination of environmental and genetic factors rather than a specific hereditary cause. A "hereditary neoplasm" is defined as an autosomal, dominant trait that is the direct expression of an inherited defect. This type of neoplasm occurs less frequently than the nonfamilial type of neoplasm; it tends to develop earlier in life and from multiple foci within organs.[10] Good examples of hereditary neoplasms are familial breast[11] and colorectal cancer.[12]

Attempts to elucidate the familial nature of prostate cancer began approximately 40 years ago after one study showed a higher incidence of prostate cancer in the close relatives of patients with prostate cancer than in those of control patients.[13] Further case-series and case–control studies found familial clustering of patients with prostate cancer.[3,4,14–16] Subsequent reports showed that, in some families, cases of prostate cancer follow a Mendelian pattern of inheritance.[17,18] The implications of these findings are only starting to become clear.

This systematic review puts the current knowledge about hereditary aspects of prostate cancer into perspective and evaluates the importance of family history in history taking and screening of men for prostate cancer.

Data sources and selection

MEDLINE was searched for articles in English or French published between Jan. 1, 1956, and Oct. 31, 1994, with the use of MeSH headings "prostatic neoplasms," "genetics" and "chromosomes." Additional references were selected from the bibliographies of articles found through the search. Ten case–control studies that investigated the incidence of prostate cancer and relative risk (RR) of such cancer in the families of men with this disease, compared with a control group without this history, were selected for critical analysis. Only studies in which prostate cancer was diagnosed on the basis of histologic tests were included. Animal investigations were excluded.

Findings

Early case–control studies

Numerous case–control studies have been conducted to substantiate the familial nature of prostate cancer. The validity of the evidence from these studies varies greatly owing to differing sample sizes, populations and quality of data analyses. Despite these limitations, the support for a genetic component in the development of prostate cancer has been consistent. Several studies (Table 1) have shown a higher incidence of prostate cancer among the relatives of cases (men with prostate cancer) than among the relatives of controls (men or women without such cancer).

A study of data from the California Tumour Registry, published in 1973, showed a higher incidence of prostate cancer among families of cases with prostate cancer confirmed by histologic tests (8/129) than among families of control patients with conditions that did not involve the genitourinary system or cancer, who were matched with cases for age and race (1/132, $p < 0.01$).[19] The family histories were obtained from standardized questionnaires and confirmed by hospital records or physician reports. This was the first study to reveal a statistically significant difference between the families of cases and those of controls.

A study published in 1974 described a high ratio of family members with prostate cancer among cases with a diagnosis of prostate cancer confirmed by histologic tests (12/210) in comparison with the ratio among control inpatients with conditions that did not involve the genitourinary system or cancer, who were matched with cases for age and race (2/215, $p < 0.01$).[7] Prostate cancer in controls was ruled out by a normal serum level of prostatic acid phosphatase and a negative result of a digital rectal examination (DRE). The incidence of prostate cancer among family members was verified by contact with physicians or examination of hospital records. This investigation confirmed the previous finding of familial clustering of prostate cancer.

A 1977 review of patients with prostate cancer admitted to hospitals in the Minneapolis and St. Paul, Minn., region showed that the incidence of prostate cancer among the families of cases (6/36) was greater than that among the families of inpatient controls matched for age and sex (3/41, not significant) and in the population (0/35, $p < 0.05$).[6] However, this study had two deficiencies: the failure to rule out the possibility of prostate cancer among controls and the small samples.

A study published in 1985 investigated 150 cases selected from a tumour registry or from hospital records who had a diagnosis of prostate cancer before 62 years of age; their brothers had a fourfold higher relative risk of prostate cancer than their brothers-in-law or other men in Utah.[20] The diagnosis of prostate cancer was confirmed by examination of hospital records. The investigators eliminated pairs of brothers diagnosed with prostate cancer during the same year. The generalizability of this study is limited because cases were restricted to those 62 years of age or less and because of the elimination of selected pairs of brothers.

Although all of these reports showed a higher incidence of prostate cancer among the families of cases than among those of controls, the actual difference in incidence varied. This variation resulted from a combination of factors including differences in study design, sample sizes, patient populations and data-collection methods. Furthermore, all of these studies were subject to possible recall bias (i.e., patients with prostate cancer may be more likely than controls to recall a family history of the disease).

As a result of the biases inherent in these early case–control studies, they failed to provide conclusive evidence separating genetic from environmental components in the development of prostate cancer. They did, however, serve to increase interest in the topic as well as to stimulate more rigorous investigations.

Recent case–control studies

More recent case–control studies have provided convincing evidence that strongly supports the familial nature of prostate cancer. In one study a self-report risk-factor questionnaire was given to all patients at a cancer treatment centre in the United States.[21] From the respondents, the investigators drew a case group with prostatic adenocarcinoma confirmed by histologic tests and a control group of patients matched with cases for age, sex and race who had cancer other than prostate cancer. The family history included a relative with prostate cancer more often in the case group than in the control group (13.0% v. 5.7%, $p = 0.01$). The overall age-adjusted RR for men with a first-degree relative with prostate cancer was significantly elevated, at 2.41 ($p = 0.001$, 95% confidence interval [CI] 1.30 to 4.47). Men with a second-degree relative who had had prostate can-

Table 1: Studies comparing the incidence of prostate cancer among families of cases and controls

Study	Setting	Format	No. of families with a history of prostate cancer/total no. of families (%) Cases	Controls	*p* value
Schuman et al[6]	Hospital	Interview	6/36 (16.7)	3/41 (7.3)* 0/35 (0)†	NS‡ < 0.05
Krain (1974)[7]	Hospital	Interview	12/210 (5.7)	2/215 (0.9)	< 0.01
Krain (1973)[19]	Tumour registry	Questionnaire	8/129 (6.2)	1/132 (0.8)	< 0.01

*Hospital-based control group.
†Population-based control group.
‡NS = not significant.

cer had an elevated but not statistically significant risk (RR 2.13; 95% CI 0.80 to 5.70).

This study's methods and case and control samples were well described. The use of a control group with cancer may have decreased the possible recall bias. Calculation of the age-adjusted relative risk increased its internal and external validity. Unfortunately, the reported incidence of prostate cancer among the families was not confirmed through histologic tests or examination of patient records.

Similarly, a higher incidence of prostate cancer among the first-degree relatives of cases than among those of controls (15% v. 8%, $p < 0.001$) was observed in a review of 741 consecutive patients who underwent radical prostatectomy.[22] The control group was composed of the patients' spouses or female companions. The RR, determined through a logistic regression analysis and adjusted for age, was higher both for cases with one affected first-degree relative (RR 2.0, 95% CI 1.2 to 3.3) and for those with one affected second-degree relative (RR 1.7, 95% CI 1.0 to 2.9). The diagnosis of prostate cancer in the relatives was validated by direct telephone contact with the relative in question or examination of medical records.

Further conditional logistic regression analysis of these case families showed that RR increased as the number of relatives affected increased.[22] The RR of prostate cancer for men with one affected relative was 2.2 (95% CI 1.4 to 3.5), with two affected relatives 4.9 (95% CI 2.0 to 12.3) and with three or more affected relatives 10.9 (95% CI 2.7 to 43.1).

The sample and methods used in this investigation were well described. The choice of control group may have served to reduce recall bias, since patients' spouses are probably more aware of prostate cancer than population-based controls. Furthermore, the controls could not be affected by the disease in question because they were women. The calculation of age-adjusted RR improved the validity of the study. The conditional regression analysis provided new information concerning the increasing RR as the number of affected family members increased. However, the method of recruiting cases may have resulted in selection bias because of the elimination of cases who were not candidates for surgery (i.e., those with metastatic cancer or unrelated health problems and those of an advanced age).

Two Canadian studies have added to the evidence supporting a familial component of prostate cancer. An investigation in Quebec involved 140 francophone hospital inpatients and 101 population-based controls matched with cases for age and sex.[3] There was a large difference in the incidence of prostate cancer among the families of the two groups; it was 15% among those of cases and only 2% among those of controls ($p < 0.001$). The RR of prostate cancer for men with one to four first-degree relatives with the disease was 8.73 (95% CI 2.00 to 38.17).

This study's population and methods were described adequately. All familial histories of prostate cancer were confirmed by a review of histologic test results. Neither age-adjusted RRs nor the RRs associated with varying numbers of affected relatives were calculated. In this study the investigators did not limit calculations to cases with one or two affected relatives, as had been done in other studies. This may explain the larger RR shown.[4,9,22] As well, limiting the case group to francophones could have led to a significant selection bias if this ethnic group were prone to familial clustering of prostate cancer or hereditary prostate cancer.

In the other Canadian study the investigators used the Alberta Cancer Registry to identify 382 cases and compared these with 625 population-based controls matched with cases for age and sex.[4] It confirmed a higher RR of prostate cancer for those with an affected first-degree relative than for those without. If the relative with prostate cancer was the case patient's father, the RR was 3.12 ($p < 0.01$). If he were any other first-degree relative, it was 3.32 ($p < 0.001$). In this investigation the population and methods were well described, and the use of population-based cases and controls increased the generalizability of the results. Cases were confirmed through histologic tests, but the reported incidence of cancer among family members was not. Age-adjusted analysis was not performed.

These reports clearly show a higher risk of prostate cancer among men who have other affected first-degree relatives than among those who do not (Table 2). It is tempting to try to combine the results of these case–control studies in order to yield a single overall risk. However, there are many inherent differences among the studies, including the selection of cases and controls as well as methods of calculating risk. Hence, pooling the outcomes could result in a misleading estimate of RR. For example, the investigation conducted in Quebec[3] found an RR up to four times greater than that found in other studies,[4,21,22] probably as a result of the potential biases discussed earlier. It is also unsuitable to combine the investigation involving the risk if one's father or other first-degree relatives had had prostate cancer[4] with other reports in which the risks for men with first-degree and second-degree relatives with the disease were given.[21,22] The two studies with the greatest validity are those in which the age-adjusted risks were calculated.[21,22] These report similar results: an RR for men with first-degree relatives with prostate cancer of 2.41 (CI 1.30 to 4.47)[21] and of 2.0 (CI 1.2 to 3.3)[22] and an RR for those with second-degree relatives with the disease of 2.13 (CI 0.80 to 5.70)[21] and of 1.7 (CI 1.0 to 2.9).[22]

The strong statistical analyses conducted as part of

these investigations were important in substantiating the familial clustering observed in earlier studies. However, they defined a familial, not a hereditary, component of the disease. These studies laid the groundwork for further decisive investigations into the hereditary nature of prostate cancer.

Hereditary prostate cancer

A landmark study by Carter and associates[17] clarified the Mendelian pattern of inheritance underlying some cases of prostate cancer. Proportional hazards were calculated and segregational analyses performed with the use of data from a sample of 691 families drawn from 740 consecutive cases of men who underwent radical prostatectomy at a US hospital between 1982 and 1989.

In the segregation analysis five models of disease transmission were tested against a general, unrestricted model. The five models tested were sporadic and environmental models as well as three types of Mendelian inheritance models: codominant, dominant and recessive. The model that best explained the observed distribution of prostate cancer in the families studied involved a dominant, disease-producing allele that is rare but highly penetrant.[17] The investigators estimated that this inherited form of prostate cancer accounts for 43% of early-onset disease (in men of less than 55 years of age) and 9% of all prostate cancer in men up to 85 years of age. The results of the proportional hazards analysis suggested that having several family members with prostate cancer and early onset of disease in the case were the most significant predictors of increased risk among relatives.[17]

This is not the first study to find a relation between the risk of prostate cancer and the number of affected family members as well as age at diagnosis. Steinburg and collaborators[22] found increased risk with an increasing number of family members with prostate cancer. Conditional logistic regression analysis of case families yielded RRs of 2.2 (95% CI 1.4 to 3.5) for men with one first-degree relative with prostate cancer, of 4.9 (95% CI 2.0 to 12.3) for men with two such relatives and of 10.9 (95% CI 2.7 to 43.1) for men with three or more such relatives. Some studies found either no difference between men in case and control families in the mean age at diagnosis[21,22] or that a familial predisposition was more apparent in older cases.[3]

The investigators refined these analyses to aid in future research and clinical applications involving hereditary prostate cancer.[18] They also proposed a definition of "hereditary" prostate cancer, based on age at onset and the distribution of cases in a family, that was intended to capture families that fit the autosomal, dominant model. A hereditary prostate cancer group was defined by one of the following three conditions: (1) a cluster of three or more affected relatives in a nuclear family, (2) the occurrence of prostate cancer in each of three generations in either the patient's paternal or maternal line or (3) a cluster of two relatives affected at an early age (55 years or less). A "familial" group was defined by a family history of prostate cancer without any of the other stated criteria. "Sporadic" prostate cancer families included only one affected family member.

Studies of the genetic aspects of prostate cancer have focused on abnormalities in chromosomes 7, 8p, 10q and 16q.[12,23–25] Identification of families with hereditary prostate cancer permits further research into gene mapping and genetic alterations involved in prostatic carcinogenesis. Such knowledge should provide important insights into the causes of prostate cancer in the population as well.

Therapeutic implications

A detailed review of the controversies concerning screening for prostate cancer is beyond the scope of this article. However, we recommend, in otherwise healthy men 50 to 70 years of age with urinary symptoms or a strong desire to know whether they have prostate cancer, an annual DRE and a test for the serum level of prostate-specific antigen (PSA). We also recommend

Table 2: Studies comparing estimated risks of prostate cancer among men with affected relatives

Study	No. of cases	No. of controls	Setting	Format	Relative	Relative risk	95% CI*
Ghardirian et al[3]	140	101	Hospital	Interview	First-degree‡	8.73	2.00–38.17
Fincham et al[4]	382	625	Insurance and cancer registry	Interview	Father	3.12	1.53–6.38
					Other first-degree	3.32	1.87–5.88
Spitz et al[21]†	378	383	Hospital	Questionnaire	First-degree	2.41	1.30–4.47
					Second-degree	2.13	0.80–5.70
Steinberg et al[22]†	692	653	Hospital	Interview	First-degree	2.0	1.2–3.3
					Second-degree	1.7	1.0–2.9

*CI = confidence interval.
†Age-adjusted risk estimate.
‡Calculated for one to four affected first-degree relatives.

that these screening manoeuvres be started at 40 years of age for men with at least one first-degree relative with prostate cancer. In all cases the patient should be informed of the subsequent decisions or actions to be taken if there is an abnormal result of the DRE or of the test for the serum PSA level. The benefits of such a policy have yet to be proven.

Elucidating the hereditary nature of prostate cancer permits targeted evaluation and improved positive predictive values of diagnostic tests as a result of identification of a population at greatest risk. This effect has already been shown by McWhorter and colleagues,[26] who emphasized the importance of testing first-degree relatives of patients with prostate cancer. They evaluated patients between 55 and 80 years of age who were from families with two affected brothers. Previously unsuspected and clinically relevant tumours were found in eight men (24% of the sample), whereas only one such tumour would normally be expected in an equivalent sample of men ($p < 0.01$).

Conclusions

Many factors have been implicated in prostate cancer. Numerous case–control studies have established that a family history increases the risk of this disease. The recent demonstration of a Mendelian pattern of inheritance of a rare, dominant, highly penetrant allele that accounts for an estimated 43% of early-onset (at less than 55 years of age) and 9% of all prostate cancer cases diagnosed by 85 years of age is a major breakthrough.[17] As a result, there is better potential for more directed research into the carcinogenesis of prostate cancer, and refinements in the current screening practices for this common disease are expected. On the basis of the evidence, we recommend that evaluation for prostate cancer should start earlier for men with at least one first-degree relative with prostate cancer than for those without such a family history.

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