Higher Frequency of Familial Clustering of Prostate Cancer in French-Canadian Men

Edith Filion,* Daniel Taussky, Jean-Paul Bahary and Christine M. Maugard

From the Département de Radio-Oncologie, Centre Hospitalier Université de Montréal (EF, DT, JPB), Département de Radiologie, Radio-Oncologie, Médecine Nucléaire (DT, JPB) and Département de Médecine (CMM), Université de Montréal, Service de Médecine Génique, Hôtel-Dieu Centre Hospitalier Université de Montréal (CMM) and Centre de Recherche Centre Hospitalier Université de Montréal (CMM), Montréal, Québec, Canada

Purpose: Prostate cancer is the second cause of cancer related death in North American men. We investigated the frequency of familial clustering in a French-Canadian population of prostate cancer cases.

Materials and Methods: Between October 2004 and September 2005, 179 consecutively seen patients with localized prostate cancer identified each of their parents as being of French-Canadian descent. They were asked for their family history of cancer in first-degree relatives, age at diagnosis, whether affected relatives were alive, age and markers of tumor aggressiveness, including prostate specific antigen, Gleason and disease stage. ANOVA was used to compare the distribution of quantitative factors according to qualitative factors identified in our population. Differences between qualitative factors were assessed by the Fisher exact test. All p values were 2-sided.

Results: Mean age at diagnosis was 67 years. A total of 45 French-Canadian patients (25.1%) had at least 1 first-degree relative with prostate cancer, including 34 (19%) with 1 first-degree relative, 9 with a father-son pair, 25 with a brother-brother pair and 11 (6.1%) with at least 2 first-degree relatives. In our series the frequency of familial clustering defined by at least 1 relative with prostate cancer was high. We found a higher percent of French-Canadian men with at least 1 first-degree relative with prostate cancer than what was previously reported for an unselected population in Canada (25.1% vs 14.7%, $p < 0.0001$).

Conclusions: Those preliminary results open a new perspective to a better understanding of familial prostate cancer in the Province of Quebec.

Key Words: prostate; prostatic neoplasms; genetic diseases, inborn; Quebec; risk

Of the potential factors contributing to prostate cancer genetic factors are a major identified risk factor.[1–4] Familial clustering of prostate cancer has frequently been reported in populations of different origins.[1,2,4] In North America approximately 10% to 15% of men with prostate cancer report at least 1 affected relative.[3,4] The prostate carcinoma risk increases with the number of affected close relatives and it is inversely related to patient age at diagnosis.

Of these cancers 5% to 10% are thought to be associated with inherited major predisposing genes.[1,2] To date despite the localization of several susceptibility loci success in identifying high risk susceptibility genes has been limited. Nonetheless, multiple strong candidate susceptibility genes have been described, namely *BRCA1*,[5] *BRCA2*,[5] *RNASEL*,[6] *NBS1*,[7] *KLF6*[8] and *MSR1*.[9] Recent experimental evidence supports the hypothesis that some familial risks may be due to the inheritance of multiple minor susceptibility genetic variants, as reviewed by Simard et al,[10] and Coughlin and Hall.[11]

In the search for genetic and environmental factors implicated in disease susceptibility French-Canadian descendants hold special interest among the Canadian population. Almost 80% of the individual gene diversity in the French-Canadian population originates from founders who settled in Nouvelle-France in 1600.[12] More than 20 inherited diseases and/or syndromes were reported in this population and they were associated with a founder effect, namely early onset breast cancer predisposition.[13] In a previous study of patients treated with radical prostatectomy for prostate cancer in the Province of Quebec the incidence of familial aggregation of cancer was shown to be significantly higher in relatives of patients identifying themselves as French speaking than in relatives of patients identifying themselves as English speaking.[14] We investigated the frequency of prostate cancer in first-degree relatives of French-Canadian patients with prostate cancer who were recruited at the radiation oncology clinic at Notre-Dame Hospital Centre Hospitalier Université de Montréal, Montreal, Province of Quebec, Canada.

PATIENTS AND METHODS

Between October 2004 and September 2005, 179 consecutive patients (index cases) referred to our radiation oncology

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* Correspondence: Centre Hospitalier Université de Montréal Hôpital Notre-Dame, 1560 Sherbrooke Est, Montréal, Québec, Canada, H2L4M1 (telephone: 514-890-8254; FAX: 514-412-7537; e-mail: edith.filion@umontreal.ca).

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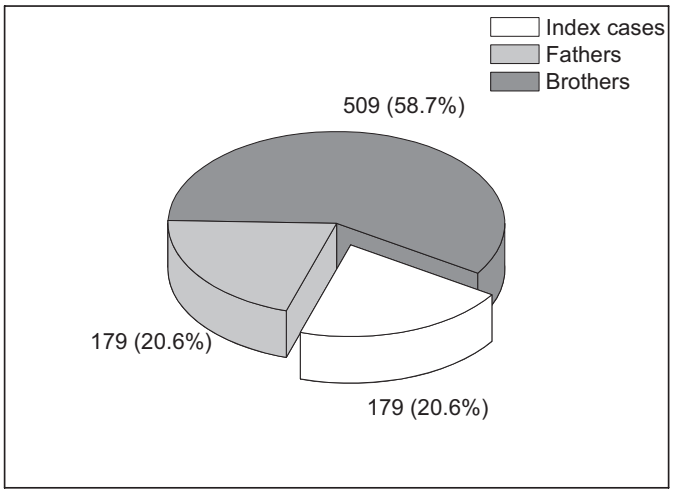

FIG. 1. Distribution of male population

clinic at Centre Hospitalier Université de Montréal were included in this study. To be included in the study patients confirmed that each parent was of French-Canadian descent. Patients had histologically confirmed prostate cancer and 2 had metastatic disease at diagnosis.

Patients were questioned by a physician on the size of their sibship and the history of cancer in first-degree relatives. When applicable, the site of cancer, age at diagnosis and death, and cause of death were recorded. Data analyses in this study were based on this questionnaire. Data were recorded as reported by index cases according to their family knowledge. Markers of the cancer aggressiveness of index cases at diagnosis, including prostate specific antigen, disease stage and Gleason, were also recorded when available.

Statistical Analyses

Analysis was done using StatView®, version 5.0. ANOVA was used to compare the distribution of quantitative factors according to the different qualitative factors identified in our population. Differences between qualitative factors were assessed by the exact Fisher test. All p values were 2-sided.

RESULTS

Information was documented according to the physician questionnaire on 858 males, including 179 index cases, 509 brothers and 179 fathers (fig. 1). Table 1 lists patient characteristics. Mean age at diagnosis was 67.5 years (range 43 to 84) for the whole group. A subgroup of patients who underwent surgery as primary treatment received radiotherapy at relapse. This subgroup had a significantly younger age at diagnosis than patients who received radiotherapy as primary treatment (63.8 vs 68.3 years, $p = 0.0004$). No significant difference in age at diagnosis was observed in index cases according to the familial history of cancer ($p = 0.74$).

Overall 179 French-Canadian index cases were assessed with a mean of 2.84 brothers (range 0 to 9). Of the patients 21 (11.7%) did not have a brother, while 37 (20.7%) had 5 or more. A total of 45 patients (25.1%) reported at least 1 first-degree relative with prostate cancer (fig. 2). Of these 45 patients 34 (18.9%) had only a single first-degree relative with prostate cancer, including 9 (5.0%) with an affected father and 25 (13.9%) with an affected brother, while 11 (6.1%) had at least 2 first-degree relatives with the disease and 3 (1.7%) had more than 2 (fig. 2). By calculating for each family the ratio of the total number of males with prostate cancer to the total number of males registered we examined the frequency of familial clustering independently of sibship size. Thus, this ratio was significantly higher in families with at least 1 relative with prostate cancer than in families with no affected relatives ($p < 0.001$). Similarly it was higher in families with at least 2 affected relatives than in families with 0 or 1 affected relative ($p < 0.001$, table 2).

Most index cases had early stage prostate cancer, that is clinical T stage less than T2b, Gleason less than 7 and prostate specific antigen less than 10 ng/ml (table 3). Table 3 shows the distribution of prognostic factors according to treatment modality. At diagnosis prostate cancer in patients in the surgical treatment group was at an earlier stage, as expected. We did not find any difference in the distribution of prognosis factors according to the family history of cancer (table 4).

DISCUSSION

Age is established as one of the strongest risk factors for prostate cancer along with family history and race. In our hospital based series age at diagnosis in our index cases is comparable to that in the Iowa cohort[15] (43 to 84 and 43 to 86 years, respectively). We did not currently identify any difference in mean age at diagnosis between patients with at least 1 affected relative and patients without any affected relatives (table 1). The only identified, statistically significant difference in mean age at diagnosis was associated with a difference in treatment modalities rather than with the number of affected relatives. Generally the mean age of patients treated with initial radiotherapy is greater than

TABLE 1. *Index case age distribution at diagnosis by familial history and treatment category*

Categories	No. Cases	Mean ± SD Age (Range)	p Value (ANOVA F test)
Familial prostate Ca history:			0.92 (not significant)
Whole group	179	67.52 ± 6.45 (43–84)	
No affected relative	134	67.49 ± 6.40 (43–84)	
At least 1 affected relative	45	67.60 ± 6.68 (51–78)	
Treatment:			0.0004 (significant)
Whole group	179	67.52 ± 6.45 (43–84)	
Initial radiotherapy	148	68.29 ± 6.42 (43–84)	
Radiotherapy at relapse	31	63.84 ± 5.30 (54–74)	
Familial prostate Ca history initial radiotherapy subgroup:			0.74 (not significant)
Whole subgroup	148	68.29 ± 6.42 (43–84)	
No affected relative	108	68.40 ± 6.34 (43–84)	
At least 1 affected relative	40	68.00 ± 6.72 (51–78)	