Early Age at Diagnosis in Families Providing Evidence of Linkage to the Hereditary Prostate Cancer Locus (HPCI) on Chromosome 1

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Abstract

In a recent study of 91 families having at least three first degree relatives with prostate cancer, we reported the localization of a major susceptibility locus for prostate cancer (HPCI) to chromosome 1 (band q24; J. R. Smith et al., Science (Washington DC), 274: 1371–1373, 1996). There was significant evidence for locus heterogeneity, with an estimate of 34% of the families being linked to this locus. In this report, we investigate the importance of age at diagnosis of prostate cancer and number of affected individuals within a family as variables in the linkage analysis of an expanded set of markers on 1q24. Under two different models for the prostate cancer locus, we find that the evidence for linkage to HPCI is provided primarily by large (five or more members affected) families with an early average age at diagnosis. Specifically, for 40 North American families with an average age at diagnosis <65 years, the multipoint lod score is 3.96, whereas for 39 families with an older average age at diagnosis, this value is ~0.84. Assuming heterogeneity, the proportion of families linked is 66% for the 14 families with the earliest average ages at diagnoses, but it decreases to 7% for the families with the latest ages at diagnoses. A similar age effect is observed in 12 Swedish pedigrees analyzed. To test the hypotheses generated by these analyses, we examined an additional group of 13 newly identified prostate cancer families. Overall, these families provided additional evidence for linkage to this region (nonparametric linkage Z = 1.91; F = 0.04 at marker D1S1660), contributed primarily by the families in this group with early age at diagnosis [nonparametric linkage Z = 2.50 (P = 0.01) at D1S422]. These results are consistent with the existence of a locus in this region that predisposes men to develop early-onset prostate cancer.

Introduction

In contrast to cancers of the breast and colon, little is known about genes that control genetic susceptibility to prostate cancer. Recently, a genome-wide scan for linkage in a series of prostate cancer families provided evidence for a prostate cancer susceptibility gene (hereditary prostate cancer 1 or HPCI) on chromosome 1 (1). In most inherited cancer syndromes, cases resulting from the action of altered susceptibility genes tend to be diagnosed significantly earlier than sporadic cases (2). For prostate cancer, segregation analysis suggests that the same tendency exists, although the mean age at diagnosis in families with a putative inherited form of prostate cancer is projected to be only 6–8 years younger than in sporadic cases (3, 4), making the use of age at diagnosis as an indicator of genetic etiology problematic. Indeed, linkage studies of prostate cancer in general are hindered by several related problems. A high lifetime incidence of disease in men in the United States (~15%; Ref. 5), along with an estimated 90% of the cases being sporadic in etiology (3), results in a potentially significant problem with phenocopies in familial clusters of prostate cancer. This problem may be particularly relevant in families with multiple men diagnosed with prostate cancer within the last 8 years, an interval in which the incidence rates for this disease have increased more than 3-fold primarily because of increased detection (6).

In this report, we investigate the importance of age at diagnosis of prostate cancer and number of family members affected as variables in the linkage analysis of markers on 1q24–25. We find that the evidence for linkage to HPCI is provided primarily by large (five or more members affected) families with an early average age at diagnosis. The positive effect of early age at diagnosis on the linkage results is also observed in an analysis of an additional group of newly identified prostate cancer families, providing additional evidence of the existence of a locus on chromosome 1 that predisposes men to develop early-onset prostate cancer.

Materials and Methods

Families. All 91 families with clusters of prostate cancer, 79 North American and 12 Swedish, that were included in the first report of linkage to HPCI (1) are included in this study. A majority of these families were ascertained through referrals from physicians in either North America or Sweden; however, some families were recruited from earlier epidemiological studies (7) and through news articles. Age at diagnosis of prostate cancer was confirmed either through medical records or from other independent sources. An additional 13 pedigrees, subsequently collected in the United States, were analyzed in this report for the first time.

Techniques of preparing DNA and genotyping were described in detail in an earlier report (1, 8). The markers applied were derived from the Genome Data Base (Johns Hopkins University School of Medicine, Baltimore, MD). Marker data were obtained for the 40 polymorphic loci available in the Genome Data Base spanning the ~25-cM interval between D1S2799 and D1S1660. A list of markers used is available from the authors upon request.

Statistical Methods. Standard multipoint parametric likelihood analysis was performed using VITESSE (9) using the same three markers in the region 1q24–25 (D1S2883, D1S158, and D1S422) as described by Smith et al. (1). Genehunter was used as described previously (1, 10) to perform parametric and nonparametric multipoint analysis of the data from all 40 markers in the 1q region. Allele frequencies for the markers were estimated from independent individuals in the families and unrelated individuals separately for the North American and Swedish families. The admixture test as implemented in HOMOG (11) was used to test for genetic heterogeneity. The age at diagnosis for each affected individual within the pedigree was included to calculate the average age at diagnosis.

Two different models (A and B) were used in the parametric analysis. In both models, prostate cancer susceptibility is conferred by an autosomal dominant allele, with a population frequency of 0.003 (3). Model A assumed a penetrance rate of 15%, regardless of age, whereas all unaffected men under 75 and all women...
Table 1 Penetrance values used in the parametric linkage analyses\textsuperscript{a}

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Penetrances of genotype (d^2)</th>
<th>dd</th>
<th>dD</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 49)</td>
<td>0.00001</td>
<td>1.0000</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>0.000061</td>
<td>0.0018</td>
<td>0.0018</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>0.00032</td>
<td>0.0030</td>
<td>0.0030</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>0.0082</td>
<td>0.0400</td>
<td>0.0400</td>
<td></td>
</tr>
<tr>
<td>(\geq 80)</td>
<td>0.0086</td>
<td>0.0151</td>
<td>0.0151</td>
<td></td>
</tr>
<tr>
<td>Unaffected males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 49)</td>
<td>0.00019</td>
<td>0.0092</td>
<td>0.0092</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>0.0032</td>
<td>0.0600</td>
<td>0.0600</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>0.022</td>
<td>0.2500</td>
<td>0.2500</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>0.079</td>
<td>0.6100</td>
<td>0.6100</td>
<td></td>
</tr>
<tr>
<td>(\geq 80)</td>
<td>0.16</td>
<td>0.8860</td>
<td>0.8860</td>
<td></td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) All women were assumed to be of unknown phenotype; \(q = 0.003\) in both models.

The data for these liability classes were derived from the segregation analysis by Carter et al. (3), and age-specific population incidences were taken from SEER (5). The penetrance values used in the linkage analysis for both models are summarized in Table 1.

Results and Discussion

Two models were used for the analysis of marker data: the first (model A) has a phenocopy rate that is age independent and is the model originally used in the analysis by Smith et al. (Ref. 1; see “Materials and Methods”), and the second (model B) uses additional liability classes based on age-dependent penetrance estimates for gene carriers and sporadic cases from segregation analysis (3) and SEER incidence data (5), respectively (Table 1). Instead of having a fixed rate for phenocopies, this second model increases the likelihood of a case being a phenocopy with increasing age.

For model A, the overall multipoint lod for all 91 families was +3.67. For the age-dependent model (model B), this value is +2.60 (Table 2). This decrease in lod score for model B indicates that older cases of prostate cancer contribute significantly to the lod score observed with model A. Regardless of which model was used, however, the evidence for linkage to HPC1 is stronger in families with a younger age at diagnosis of prostate cancer. For example, if one examines the subset of families in which the cases have an average age at diagnosis under the mean age at diagnosis for the group as a whole (under 65 for the North American families and under 70 for the Swedish families), similar lod scores are obtained with both models: +4.52 (+3.96 in the North American and +0.56 in the Swedish families, respectively) with model A and +4.27 (+4.03 and +0.24, respectively) with model B. (The difference in median ages in the North American and Swedish families is explained most likely by the different diagnostic methodologies in these countries.)

Table 2 Maximum multipoint lod scores using D1S2883, D1S158, and D1S422\textsuperscript{a}, subdivided by average age of diagnosis

Two different models for the parametric analysis were used (models A and B).

<table>
<thead>
<tr>
<th>Average age at diagnosis (No. of families)</th>
<th>Lod Score</th>
<th>Lod Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.7–59.9 (14)</td>
<td>+1.95</td>
<td>2.70 (0.66)</td>
</tr>
<tr>
<td>60–64.9 (26)</td>
<td>+2.01</td>
<td>3.60 (0.54)</td>
</tr>
<tr>
<td>65–69.9 (29)</td>
<td>-0.70</td>
<td>0.40 (0.14)</td>
</tr>
<tr>
<td>70–73.8 (10)</td>
<td>-0.14</td>
<td>0.01 (0.07)</td>
</tr>
<tr>
<td>Total (79)</td>
<td>+3.12</td>
<td>4.80 (0.33)</td>
</tr>
<tr>
<td>Model B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.7–59.9 (14)</td>
<td>+1.53</td>
<td>2.59 (0.98)</td>
</tr>
<tr>
<td>60–64.9 (26)</td>
<td>+2.50</td>
<td>2.90 (0.86)</td>
</tr>
<tr>
<td>65–69.9 (29)</td>
<td>-1.16</td>
<td>0.15 (0.20)</td>
</tr>
<tr>
<td>70–73.8 (10)</td>
<td>-0.50</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Total (79)</td>
<td>+0.55</td>
<td>3.50 (0.53)</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) Calculated using VITESSE.

Fig. 1. Cumulative lod scores (\(\Phi\)) by pedigree as a function of average age at diagnosis of prostate cancer. Multipoint lod scores at D1S422 using model A with markers D1S2883, D1S158, and D1S422 for each of 79 North American pedigrees are plotted as a function of increasing average age at diagnosis within the pedigree.
To further characterize the evidence for linkage to chromosome 1, additional markers were genotyped in the 79 North American families, such that marker data were obtained for 40 polymorphic loci spanning the ~25-cM interval between D1S2799 and D1S1660 on 1q24. Nonparametric multipoint analysis of these data using Genehunter provided similar results to that obtained above in that significant evidence was obtained for linkage in the group of families as a whole (NPL \( Z = 4.50 \) at D1S422), although this evidence was found primarily in the families with average age at diagnoses under 65 (NPL \( Z = 5.57 \)), rather than in families with later average age at diagnoses (NPL \( Z = 0.70 \)). Similarly, this trend was reflected in the multipoint lod scores, calculated using Genehunter with model A and all marker data available for this region (Table 3).

The impact of the number of affected individuals within a given family on the linkage analysis was examined in the 79 North American families. These results are summarized in Table 3. This analysis indicates that the majority of evidence for linkage to chromosome 1 is provided by the families with the most affected members. This is particularly prominent in the subset of 21 families that have an average age at diagnosis under 65 as well as five or more family members affected with prostate cancer (NPL \( Z = 6.58 \), lod = 5.10, and \( \alpha = 0.51 \), at D1S422 for this group).

To test the hypothesis of linkage of HPC1 to 1q24–25 overall and whether evidence for this linkage is found primarily in families with early age at diagnosis, we collected an additional 13 North American families for linkage analysis. These families were similar to our original group in that they are predominantly Caucasian (1 of 13 being African American) with an average of five affected individuals and an average age at diagnosis of 66. An average of 3.6 affected individuals per family were genotyped at the 40 loci in the HPC1 region of 1q24. Whereas a maximum multipoint NPL \( Z \) score of 1.91 (\( P = 0.04 \)) at D1S1660 was obtained for the 13 families overall, the five families in which the cases had an average age at diagnosis under 65 had an NPL \( Z \) score of 2.50 (\( P = 0.01 \)) at D1S422, compared to a value of \(-0.56 \) at this locus for the later-onset families.

That the evidence of linkage to HPC1 is supported primarily by cases with young age at diagnosis is similar to the patterns observed in the initial linkages to BRCA1 (12, 13) and BRCA2 (14). However, the difference in average age between sporadic and hereditary cases in breast cancer is estimated to be 20 years (2), but in prostate cancer, this difference may be only 6–8 years (3, 4). After 65 years of age, the risk of prostate cancer increases dramatically in the general population (5), and it seems reasonable to assume that a parallel increase in the phenocopy rate in families with clustering of prostate cancer also would occur, and that this would be particularly important in families with cases diagnosed at older ages. In these “older” families, there may be some prostate cancers attributable to HPC1, which is not apparent due to the small size that generally characterizes the pedigrees analyzed here, such that a single phenocopy renders the evidence of linkage undetectable.

When the HPC1 gene is isolated, mutation analysis can be performed in these families, and the validity of this notion can be tested directly.

This study has important implications in terms of other studies attempting to find linkage of prostate cancer susceptibility to chromosome 1. For example, it is apparent from this study that unless one examines a sufficient number of families that are large and have an early average age at prostate cancer diagnosis, significant evidence for linkage to chromosome 1 will most likely not be observed. However, if one focuses on large, early-onset families, one may expect to find as many as 50% of such families being linked to 1q24–25.

In summary, the evidence for linkage of familial prostate cancer to the HPC1 locus on chromosome 1 is contributed primarily by families characterized by a large number of affected members and early ages at diagnosis. Thus, as is the case with other cancer susceptibility alleles, the HPC1 locus appears to increase the risk of early-onset prostate cancer.

### References


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