Association of E-Cadherin Germ-Line Alterations with Prostate Cancer


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ABSTRACT

In our recent cancer registry-based study, the incidence of gastric carcinoma was increased up to 5-fold in male relatives of early-onset prostate cancer (PCA) patients. This association may reflect the influence of genetic factors predisposing individuals to both tumor types. Germ-line mutations of the CDH1 gene at 16q have recently been associated with familial gastric cancer. Furthermore, two genome-wide linkage studies of PCA recently reported positivity at 16q. We therefore identified families and individual patients with both gastric and PCA and investigated whether the CDH1 gene mutations were involved in cancer predisposition in these cases. Fifteen of the 180 Finnish hereditary PCA families (8.3%) had one or more gastric cancer cases. No truncating or splice site CDH1 mutations were identified by PCR single-strand conformational polymorphism in these families or in eight individual patients who had both prostate and gastric cancer. However, a novel S270A missense mutation in exon 6 of the CDH1 gene was seen in a single family with four prostate and two gastric cancers. A large-scale population-based survey indicated a higher prevalence of S270A among both familial PCA cases (3.3%; n = 120; P = 0.01) and unselected PCA patients (1.5%; n = 472; P = 0.12) as compared with blood donors serving as population controls (0.5%; n = 923). We conclude that individual rare mutations and polymorphisms in the CDH1 gene, such as S270A, may contribute to the onset of PCA and warrant further investigations in other populations. However, the CDH1 gene does not appear to explain the link between prostate and gastric cancer.

INTRODUCTION

Positive family history is one of the strongest risk factors for prostate carcinoma (1). Approximately 5–10% of PCA cases may be influenced by a germ-line predisposition (2, 3). At least seven chromosomal regions have recently been implicated to harbor PCA susceptibility genes based on linkage analysis: (a) 1q24-q25 (4); (b) 1q42-q43 (5); (c) Xq27-q28 (6); (d) 1p36 (7); (e) 20q13 (8); (f) 11p (9); and (g) 16q (10). The large number of loci found to be involved in PCA predisposition most likely reflects the substantial genetic heterogeneity of this disease. Efforts to reduce this variability have included stratification by the age of onset, number of affected relatives, or the mode of transmission in the family (11). In addition, stratification of cancer families based on the spectrum of other malignancies can be useful, as best illustrated in the search of breast cancer predisposition genes. Breast-ovarian cancer families are most often linked to the BRCA1 locus, and male breast cancer families are most often linked to the BRCA2 gene (12, 13). In epidemiological studies of PCA families, brain tumors have usually been the only tumor type, which has been overrepresented (2, 3, 14). The study by Gibbs et al. (7) applied these observations to identify 1p36 linkage in those PCA families that also had brain tumors.

Our recent population-based cancer registry study of 10,000 relatives of PCA patients with follow-up of 299,970 person years during 1953–1997 revealed increased risk of gastric cancer in male relatives of PCA patients diagnosed at an early age (≤60 years of age; Ref. 15). The highest risk of gastric cancer was detected for the male relatives of PCA patients diagnosed at an age of 55 years or less (SIR, 5.0; 95% CI, 2.8–8.2; P < 0.0001). Besides prostate and gastric cancers, no other cancer types showed any significant excess of risk. In the subgroup of male relatives of PCA patients diagnosed at an age of 55 years or less, the SIR of gastric cancer in the relatives was even higher than the SIR for PCA (15).

Epithelial E-cadherin is a cell surface glycoprotein that is responsible for Ca2+-dependent cell-cell adhesion and plays an essential role in the formation and maintenance of normal epi-

1The abbreviations used are: PCA, prostate cancer; SIR, standardized incidence rate; CI, confidence interval; HNPC, hereditary nonpolyposis colon cancer; SSCP, single-strand conformational polymorphism; HPC, hereditary prostate cancer; LOH, loss of heterozygosity; OR, odds ratio.

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CDH1 Mutations 1 and 2. HNPCC cancer syndrome is primarily associated with colorectal and endometrial cancers, but gastric cancers are also commonly seen in these families. To exclude the HNPCC phenotype as a cause for the prostate-gastric cancer association, Finnish founder mutations for the MLH1 gene were screened from members of 15 prostate-gastric cancer families and 8 patients diagnosed with both prostate and gastric cancers. Together, these two MLH1 mutations account for 51% of all Finnish kindreds with verified or putative HNPCC (28). Mutation 1 in the MLH1 gene (a 3.5-kb genomic deletion affecting exon 16 and flanking introns; Ref. 27) was detected as described by Nyström-Lahti et al. (27), except that the annealing temperature was 65°C in PCR. Mutation 2 in the MLH1 gene (a single-base change at the splice-acceptor site of exon 6; Ref. 27) was screened by minisequencing. For mutation 2 screening, exon 6 was first amplified using 100 ng of DNA, 0.2 μM both primers, 0.2 mM each deoxynucleotide triphosphate, 2 mM MgCl₂, and 2.5 units of AmpliTaq Gold (Perkin-Elmer) in a final volume of 50 μl at 95°C for 10 min, followed by 35 cycles of 94°C for 1 min, 51°C for 1 min, and 72°C for 1 min with a 5-min extension at 72°C after the last cycle. Primers for PCR were 5′-biotin-CTTTTGCCAGGACATCTT-3′ and 5′-ACAAATCTCAGAGACCCAC-3′. Minisequencing was performed as described by Syvänen (30) with a detection primer (5′-TTGTTAAAAAGGTCCTCCAC-3′). In both mutation 1 and 2 screening, the positive controls were included.

CDH1 Mutation Screening. SSCP analysis of the entire coding sequence of the CDH1 gene was performed from genomic DNA samples from 15 prostate-gastric cancer families and 8 prostate-gastric cancer patients. Primer sequences and PCR conditions were based on those described by Berx et al. (31). Genomic DNA was used at 100 ng per 25-μl reaction mixture containing 2–3 mM MgCl₂; 20 μM dATP, dCTP, dGTP, and dTTP; 1 μCi of [α-33P]dCTP (Amersham Pharmacia BioTech); 25 pmol of each primer; 1.5 units of AmpliTaq Gold; and the reaction buffer provided by the supplier (Perkin-Elmer). Radiolabeled PCR reaction products were mixed with 95% formamide dye, denatured at 95°C for 5 min, and chilled on ice. The 33P-labeled PCR products were electrophoresed at 800 V for 20 h at room temperature in a 0.8× mutation detection enhancement gel (FMC BioProducts, Rockland, ME) containing 1% glycerol or at 3 W for 12 h at 4°C using 5% polyacrylamide gel with Tris-PIPES-EDTA (pH 6.8) buffer system (32). After electrophoresis, gels were dried and exposed to Kodak BioMax MR films for 1–2 days. All samples in which a variant band was detected were sequenced using the original PCR primers with ABI PRISM 310 Genetic Analyzer (Perkin-Elmer).

Large-scale Population-based Analysis of the S270A Mutation Using Minisequencing. PCR-SSCP analysis of the CDH1 gene revealed a novel S270A missense mutation in one prostate-gastric cancer family. To examine the association of the S270A variant in PCA predisposition at the population level, we studied the frequency of the variant among population controls and PCA cases. A 246- or 135-bp fragment was first amplified using 100 ng of DNA, 0.2 μM both primers, 0.2 mM each deoxynucleotide triphosphate, 3 mM MgCl₂, and 2.5 units of

MATERIALS AND METHODS

Study Population. Personal identification codes of members of 180 Finnish HPC families (29) with two or more affected first- or second-degree relatives/family were linked to the Finnish Cancer Registry to identify those families that also had gastric cancer cases. Fifteen of the 180 families had both prostate and gastric cancer cases according to the Finnish Cancer Registry data. The cancer registry data were critical to provide both clinical and histological confirmation of diagnoses that are often very inaccurately ascertained by family questionnaires. These prostate-gastric cancer families had two or more cases of PCA and at least one case of gastric cancer per family. One PCA patient from each of the 15 families was analyzed for germ-line CDH1 mutations. In three families, the sample of the affected individual was not available, and a sample from a first-degree relative was used.

We also reviewed the database of the Department of Pathology at Tampere University Hospital to identify individual patients who were diagnosed with both prostate and gastric cancers since 1993. Of 1738 PCA patients recorded between 1993 and 1999, 18 patients had also been diagnosed with gastric cancers. Of 1738 PCA patients recorded between 1993 and 1999, 18 patients had also been diagnosed with gastric carcinoma. A DNA sample was available from eight of these prostate-gastric cancer patients.

To carry out a population-based screening of the frequency of the missense mutation S270A, the screening was extended to the following groups: (a) one affected individual from 120 Finnish PCA families with two or more affected first- or second-degree relatives (regardless of gastric cancer status); (b) 472 unselected, consecutive PCA patients from Tampere University Hospital; (c) 140 gastric cancer patients from Tampere University Hospital; and (d) 923 anonymous, unselected healthy male blood donors. DNA was extracted from whole blood using the Puregene kit (Gentra Systems, Minneapolis, MN) following the manufacturer’s protocol. DNA extractions from paraffin-embedded, formalin-fixed tissues were carried out using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Written informed consent was obtained from all patients giving a blood sample for the study. The present study was approved by the ethics committee of Tampere University Hospital and the local ethics committees of other regional hospitals. The study of HPC was also approved by the National Human Genome Research Institute Institutional Review Board.

Screening for the Specific Finnish MLH1 Founder Mutations 1 and 2. HNPCC cancer syndrome is primarily associated with colorectal and endometrial cancers, but gastric cancers are also commonly seen in these families. To exclude the HNPCC phenotype as a cause for the prostate-gastric cancer association, Finnish founder mutations for the MLH1 gene were screened from members of 15 prostate-gastric cancer families and 8 patients diagnosed with both prostate and gastric cancers. Together, these two MLH1 mutations account for 51% of all Finnish kindreds with verified or putative HNPCC (28). Mutation 1 in the MLH1 gene (a 3.5-kb genomic deletion affecting exon 16 and flanking introns; Ref. 27) was detected as described by Nyström-Lahti et al. (27), except that the annealing temperature was 65°C in PCR. Mutation 2 in the MLH1 gene (a single-base change at the splice-acceptor site of exon 6; Ref. 27) was screened by minisequencing. For mutation 2 screening, exon 6 was first amplified using 100 ng of DNA, 0.2 μM both primers, 0.2 mM each deoxynucleotide triphosphate, 2 mM MgCl₂, and 2.5 units of AmpliTaq Gold (Perkin-Elmer) in a final volume of 50 μl at 95°C for 10 min, followed by 35 cycles of 94°C for 1 min, 51°C for 1 min, and 72°C for 1 min with a 5-min extension at 72°C after the last cycle. Primers for PCR were 5′-biotin-CTTTTGCCAGGACATCTT-3′ and 5′-ACAAATCTCAGAGACCCAC-3′. Minisequencing was performed as described by Syvänen (30) with a detection primer (5′-TTGTTAAAAAGGTCCTCCAC-3′). In both mutation 1 and 2 screening, the positive controls were included.

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AmpliTaq Gold (Perkin-Elmer) in a final volume of 50 μl at 95°C for 10 min, followed by 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 45 s, with a 5-min extension at 72°C after the last cycle. Primers for PCR were 5′-biotin-CTCACCTTGTTTCCTTTCAG-3′ (produced a 246-bp fragment) or 5′-biotin-GAATTCCACCCAGGAGTTC-3′ (produced a 135-bp fragment) and 5′-AACCTTTGGGCTTGGACA-3′. Minisequencing was performed as described by Syvänen (30) with a detection primer (5′-AAGAG-CACCTTCCATGACAG-3′). Minisequencing positive results were confirmed by sequencing with ABI PRISM 310 Genetic Analyzer (Perkin-Elmer) using the same primers as in PCR.

Statistical Analysis. Statistical analyses were performed using GraphPad InStat version 2.04a (GraphPad Software) and StatView for Windows version 5.0.1. (SAS Institute Inc.). Correlations were made with two-tailed Fisher’s exact test. In addition, the OR and 95% CIs were calculated using the approximation of Woolf.

RESULTS

Clinical Characteristics of the Study Population. We identified 15 families (8.3%) with both prostate and gastric cancer among the 180 previously ascertained Finnish HPC families (29). These prostate-gastric cancer families had an average of 2.9 cases (range, 2–5 cases) of PCA and 1.4 cases (range, 1–4 cases) of gastric cancer (Table 1). Four patients in these families had both gastric cancer and PCA. The average age of PCA diagnosis in these families was 70 years (range, 45–99 years), and the average age of gastric cancer diagnosis was 72 years (range, 62–84 years). The histological type of gastric cancer was diffuse in two cases and intestinal in three cases, and the type could not be ascertained for sure in three cases.

Exclusion of HNPPC Mutations as a Cause of Prostate Cancer-Gastric Cancer Association. HNPPC families often have an excess of gastric cancers (33), and an increased risk of PCA has also been suggested (34). To exclude HNPPC families and patients, we screened the Finnish founder mutations 1 and 2 of the MLH1 gene from members of 15 prostate-gastric cancer families and 8 patients diagnosed with both prostate and gastric carcinomas. These two founder mutations cover 51% of all Finnish kindreds with verified or putative HNPPC (28). No MLH1 mutations were detected, which is compatible with the observation that there is no increase in colorectal and endometrial cancer cases in our HPC families.

Exclusion of CDH1 Mutations in Gastric-Prostate Cancer Patients and Families. Samples of the same cohort of 15 families and 8 prostate-gastric cancer patients were further screened for germ-line mutations in the 16 exons of the CDH1 gene by PCR-SSCP from genomic DNA, PCR-SSCP analysis of all 16 exons of the CDH1 gene from genomic DNA revealed no splice site or truncating mutations. One missense mutation leading to a serine (TCT)→alanine (GCT) substitution at codon 270 in exon 6 was detected in family 215 (Fig. 1). Family 215 has four PCA cases and one gastric cancer case in the paternal lineage and one gastric cancer case in the maternal lineage. Due to the lack of DNA samples from the older generation, it is impossible to discover through which line the CDH1 variant is inherited. The average age of prostate and gastric cancer diagnosis was 77 years (range, 64–99 years) and 81 years (range, 77–85 years), respectively. Three brothers diagnosed with PCA were also S270A variant carriers. The fourth brother was also a S270A variant carrier, but he did not have PCA. However, he was younger than the average age of PCA diagnosis in this family. In addition, two silent polymorphisms were frequently identified: (a) a C→T polymorphism at nucleotide 2076 (exon 13); and (b) a G→C polymorphism at nucleotide 531+10.

### Table 1 Description of 15 Finnish prostate-gastric cancer families

<table>
<thead>
<tr>
<th>Family no.</th>
<th>No. of PCA cases in family</th>
<th>Mean age (yrs) at diagnosis of PCA in family (range)</th>
<th>No. of GCA* cases in family</th>
<th>Mean age (yrs) at diagnosis of GCA in family (range)</th>
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<td>2</td>
<td>68 (67–68)</td>
<td>2</td>
<td>67 (61–72)</td>
</tr>
<tr>
<td>93</td>
<td>2</td>
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<td>65</td>
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<td>130</td>
<td>4</td>
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<td>72</td>
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<tr>
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<td>4</td>
<td>68 (50–80)</td>
<td>2</td>
<td>74 (71–76)</td>
</tr>
<tr>
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<td>2</td>
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<td>1</td>
<td>34</td>
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<td>79 (74–83)</td>
<td>4</td>
<td>73 (61–88)</td>
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<td>1</td>
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<td>2</td>
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<td>1</td>
<td>64</td>
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<td>79 (69–92)</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>905</td>
<td>2</td>
<td>55 (45–64)</td>
<td>1</td>
<td>77</td>
</tr>
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</table>

*GCA, gastric cancer.
CDH1 mutations. The mutation in exon 6 was present in the heterozygous state in the tumor, indicating that there was no LOH (data not shown). Because germ-line mutations of CDH1 have recently been associated with familial gastric cancer (17–22), we also studied the association of the S270A variant and gastric carcinoma. Increased frequencies of the S270A variant were detected among all gastric cancer patients [2 of 140 patients (1.4%); *P = 0.24] and among patients with diffuse-type gastric cancer [2 of 68 patients (2.9%); *P = 0.08], but because of the small sample size, these differences remained statistically insignificant.

**DISCUSSION**

Our search of germ-line mutations of the CDH1 gene among prostate-gastric cancer families and patients did not reveal any splice site or truncating mutations, suggesting that the CDH1 gene does not explain the PCA-gastric cancer association reported in our recent population-based study (15). Although the hypothesis was rejected because of the absence of these major mutations in SSCP analysis, the results should be interpreted with caution because of the small sample size and the 100% sensitivity in mutation detection. However, a novel S270A missense variant in the DNA sample of family members. An arrow indicates the individual initially screened for CDH1 mutations.

| Table 2: Prevalence of S270A missense substitution of the CDH1 gene among Finnish cancer patients and population controls |
|-----------------|-----------------|-----------------|
|                  | Frequency       | Relative risk   | *P*  |
|                  |                 | (95% CI)        |      |
| Familial PCA     | 3.3% (4/120)    | 6.33 (1.68–23.92) | 0.01 |
| Unselected PCA†  | 1.5% (7/472)    | 2.76 (0.87–8.76) | 0.12 |
| Familial and unselected PCA | 2.0% (10/582) | 3.21 (1.09–9.44) | 0.03 |
| Gastric cancer   |                |                 |      |
| Diffuse          | 1.4% (2/140)    | 2.64 (0.52–13.47)| 0.24 |
| Intestinal       | 2.9% (2/68)     | 5.43 (1.07–27.48)| 0.08 |
| Unknown          | 0% (0/2)        |                 |      |
| Controls         | 0.5% (5/923)    |                 |      |

† Group includes 10 familial PCA cases.
gene (23) have also been reported. E-cadherin is responsible for Ca$^{2+}$-dependent cell-cell adhesion and plays an essential role in the maintenance of normal epithelial tissue architecture (16).

Recently, two genome-wide linkage studies of PCA families suggested positivity at 16q (9, 10), the chromosomal site of the CDH1 gene. However, a direct role of the CDH1 gene in PCA predisposition has not been obtained. The present findings of a population-level association between the S270A variant and PCA suggest that rare variants of the CDH1 gene may be significant and contribute to PCA development. The extracellular domain of E-cadherin contains five tandemly arranged cadherin repeats that form four calcium-binding pockets, each between two successive repeats. Complex formation with calcium ions is required for dimerization and rigidification of E-cadherin between two successive repeats. Complex formation with calcium and provides resistance to extracellular proteases (42). In the mature protein, the missense variant S270A is located at the beginning of the second extracellular repeat (31). Although the missense variant S270A is not part of any highly conserved sequence motifs required for Ca$^{2+}$ binding (42–44) or dimerization (45, 46), the amino acid change is from polar to nonpolar and hydrophobic. The polar amino acid at position 270 is conserved in most species and also in other type I classic cadherins (31). These biochemical and evolutionary clues suggest that the S270A variant could affect protein function.

As with any genetic variants associated with a complex disease, it will be important to validate the present results on the association between the CDH1 gene and PCA in other populations. This study also highlights the fact that a number of different genetic alterations may contribute to cancer development. Therefore, it is important not to focus exclusively on finding rare, highly penetrant germ-line mutations by linkage analysis or common single-nucleotide polymorphisms that show association with disease but may have only a negligible effect on disease risk. Specific mutations and single-nucleotide polymorphisms that are disease associated may be rare, such as the S270A variant, and they may be distributed among a large number of different genes, requiring large-scale surveys with emerging DNA chip technologies (47) and very large amounts of patient materials.

In conclusion, our data suggest that the CDH1 gene does not explain the PCA-gastric cancer association. Taken together with the lack of MLH1 gene mutations and the lack of phenotypic features of the HNPCC syndrome, the results suggest that currently unknown genes may contribute to the observed link between PCA and gastric cancer. This epidemiological association may suggest an underlying common genetic defect for such prostate-gastric cancer families and may substantially facilitate linkage analyses in PCA by reducing genetic heterogeneity. At the same time, population-based association studies are warranted to evaluate the significance of individual rare mutations and polymorphisms in the CDH1 gene, such as the S270A, in PCA causation.

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