*Am. J. Hum. Genet.* 64:776–787, 1999

# Evidence for a Rare Prostate Cancer–Susceptibility Locus at Chromosome 1p36

Mark Gibbs,[1,*] Janet L. Stanford,[2,3,*] Richard A. McIndoe,[4,*,†] Gail P. Jarvik,[3,5,*] Suzanne Kolb,[2] Ellen L. Goode,[3] Lisa Chakrabarti,[4] Eugene F. Schuster,[4] Valerie A. Buckley,[1] Elizabeth L. Miller,[1,6] Susan Brandzel,[2] Sarah Li,[4] Leroy Hood,[4] and Elaine A. Ostrander[1]

Divisions of [1]Clinical Research and [2]Public Health Sciences, Fred Hutchinson Cancer Research Center, and [3]Department of Epidemiology, School of Public Health & Community Medicine, and [4]Department of Molecular Biotechnology, University of Washington, and Departments of [5]Medicine, Division of Medical Genetics, and [6]Urology, University of Washington Medical Center, Seattle

## Summary

**Combining data from a genomic screen in 70 families with a high risk for prostate cancer (PC) with data from candidate-region mapping in these families and an additional 71 families, we have localized a potential hereditary PC-susceptibility locus to chromosome 1p36. Because an excess of cases of primary brain cancer (BC) have been observed in some studies of families with a high risk for PC, and because loss of heterozygosity at 1p36 is frequently observed in BC, we further evaluated 12 families with both a history of PC and a blood relative with primary BC. The overall LOD score in these 12 families was 3.22 at a recombination fraction ($\theta$) of .06, with marker D1S507. On the basis of an a priori hypothesis, this group was stratified by age at diagnosis of PC. In the younger age group (mean age at diagnosis <66 years), a maximum two-point LOD score of 3.65 at $\theta = .0$ was observed, with D1S407. This linkage was rejected in both early- and late-onset families without a history of BC (LOD scores −7.12 and −6.03, respectively, at $\theta = .0$). After exclusion of 3 of the 12 families that had better evidence of linkage to previously described PC-susceptibility loci, linkage to the 1p36 region was suggested by a two-point LOD score of 4.74 at $\theta = .0$, with marker D1S407. We conclude that a significant proportion of these families with both a high risk for PC and a family member with BC show linkage to the 1p36 region.**

Received September 1, 1998; accepted for publication January 7, 1999; electronically published February 17, 1999.

Address for correspondence and reprints: Dr. Elaine A. Ostrander, Division of Clinical Research, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D2-190, Seattle, WA 98109-1024. E-mail: eostrand@fhcrc.org

[*] These authors contributed equally to this work.

[†] Present affiliation: Curagen Corporation, Alachua, FL.

© 1999 by The American Society of Human Genetics. All rights reserved.
0002-9297/99/6403-0015$02.00

## Introduction

Prostate cancer (PC) is the most common cancer (excluding nonmelanoma skin cancer) and the second leading cause of cancer deaths among men in the United States. In 1998 alone, PC will have been newly diagnosed in ~184,500 men, and ~39,000 men will die of the disease (Landis et al. 1998). PC incidence is highest among men in their late 60s and 70s, with 23% of the total PC population being men given a diagnosis at age <65 years and with only 4% being men given such a diagnosis at age <55 years (Stanford et al., in press).

Epidemiological data suggest that a strong familial component is involved in the etiology of at least a subset of cases of PC, particularly those diagnosed at younger ages. A family history of PC in a first-degree relative is associated with a significant two- to threefold elevation in risk (Steinberg et al. 1990; Hayes et al. 1995; Whittemore et al. 1995). These results are supported by segregation analyses (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998), which found that both early age at onset and the presence of multiple affected family members were strong predictors of risk in relatives. Carter et al. (1992) proposed that inheritance of a rare, autosomal dominant allele(s) ($q = .003$) with a high lifetime penetrance (88%) may explain PC incidence in 43% of early-onset cases (i.e., at age ⩽55 years) and ~9% of all cases of PC in the population. More recently, a population-based segregation analysis estimated a higher frequency of the dominant risk allele ($q = .0167$) and a lower lifetime penetrance, 63% (Grönberg et al. 1997*a*).

Analyses of prostate tumors have suggested the presence of PC–susceptibility loci at a number of human chromosomes, including regions of chromosomes 8, 10, 16, and 17 (Bova et al. 1993; Massenkeil et al. 1994; Cher et al. 1996; Williams et al. 1996). Thus far, however, no PC–susceptibility locus has been revealed on any of these chromosomes (Cannon-Albright and Eeles 1995), and genomewide screens of families with a high risk for PC are ongoing. By using this approach, Smith

et al. (1996) localized the first PC–susceptibility locus (*HPC1*) to chromosome 1q24-25, by linkage analysis of 91 families with a high risk for PC that were from the United States and Sweden. Smith et al. (1996) estimated that germ-line mutations in *HPC1* accounted for 34% of PC in the families described. Families predicted to carry mutations at this locus are reported to be enriched for younger ages at diagnosis, higher-grade tumors, and more advanced-stage disease at diagnosis (Grönberg et al. 1997*b*, 1997*c*), although the association with tumor characteristics remains a topic of some debate (Laniado 1998). Although two sets of data provide confirmatory evidence that *HPC1* is responsible for PC susceptibility in some families at high risk (Cooney et al. 1997; Hsieh et al. 1997), in other data sets the linkage to *HPC1* is undetectable, suggesting that issues related to locus heterogeneity at 1q24-25 are not completely understood (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998). In all likelihood, the apparently contradictory results may be reconciled, at least in part, if it is found that *HPC1* either contributes to markedly <34% of PC in high-risk families or is disproportionately responsible for disease in particular subsets of families.

Very recently, a second PC–susceptibility locus (*PCAP*) was localized to 1q42.2-43 in a set of 47 French and German families (Berthon et al. 1998), and another (*HPCX*) has been mapped to the X chromosome (Xu et al. 1998). Although findings reported by these investigators await confirmation, it is clear that the loci described thus far do not account for the majority of PC in most high-risk families ascertained to date. Thus, additional PC–susceptibility genes remain to be mapped. Toward that end, we are continuing a genomewide screen of families with a high risk for PC.

An initial analysis of our genomewide-screen data highlighted chromosome 1p36. This region is of interest in cancer genetics, for several reasons. Although it has not been reported as a region of frequent loss of heterozygosity (LOH) in prostate tumors, it has been frequently cited as a region of LOH for a variety of types of brain tumors and CNS tumors (Bello et al. 1994*b*, 1995*b*; Schleiermacher et al. 1994; Kraus et al. 1995; Maris et al. 1995; White et al. 1995; Kaghad et al. 1997). Interestingly, epidemiological studies have found an association between brain cancer (BC) and PC. Specifically, Carter et al. (1993) reported that families with hereditary PC have a significant excess of BC, and Isaacs et al. (1995) showed that such families have a significantly increased relative risk (RR) for tumors of the CNS (RR 3.02; 95% confidence interval [CI] 1.08–8.41). In a population-based family study, Goldgar et al. (1994) also found an elevated RR of 1.25 (95% CI 1.0–1.5) for BC and CNS cancer among first-degree relatives of PC probands. Thus, there appears to be a link between these two seemingly unrelated types of cancer. We report here on findings at 1p36, which appears to be responsible for inherited disease in a defined subset of families with PC that share a family history of primary BC.

## Subjects and Methods

### *Ascertainment of Families with PC*

A genomewide screen to map hereditary PC loci is being conducted in families with a high risk that were recruited nationwide as part of the Prostate Cancer Genetic Research Study (PROGRESS). Participants from eligible families are located throughout the United States, Canada, and several other countries. Eligible families must meet at least one of three criteria: three or more first-degree affected relatives, PC in three generations, and/or PC diagnosed in at least two affected siblings at age $\leqslant$60 years. National advertising, media events, and mailings to cancer support groups and urologists were used to recruit families into the ongoing study, which was initiated in July 1995. A toll-free number (1-800-777-3035) has been established to screen potential participants for their suitability. Once enrolled in the study, both affected and selected unaffected male and female family members are asked to provide a blood sample and to complete a self-administered questionnaire that obtains information on demographic factors, medical history, family size and structure, and family history of cancer. In addition, consent to access medical records related to the diagnosis and treatment of cancer is requested. All study procedures and forms are approved by the institutional review board of the Fred Hutchinson Cancer Research Center. Detailed procedures for contact of families, selection of individuals for collection, isolation of DNA, and genotyping have been summarized elsewhere (McIndoe et al. 1997; authors' unpublished data).

### *Linkage Analysis*

LINKAGE version 5.1 (Lathrop et al. 1984) was used for two-point linkage analysis. Multipoint parametric and nonparametric linkage (NPL) analyses used GENEHUNTER version 1.2 (Kruglyak et al. 1996). NPL scores used were calculated by the $NPL_{pairs}$ option, because this is expected to be more robust to phenocopies than is the $NPL_{pairs}$ option, as would be expected in a common disease such as PC.

An admixture test for heterogeneity in the data set was performed by HOMOG (Ott 1991). Parameters for the autosomal dominant transmission models are described in table 1. For both early-onset (<66 years) and late-onset ($\geqslant$66 years) pedigrees, the age-dependent penetrance functions were estimated from our larger sample of families with PC. The early-onset model was also used

## Table 1

**Genotype-Specific Penetrances for Transmission Models**

| | Frequency When Mean Age at Diagnosis Is | | | | | |
|---|---|---|---|---|---|---|
| | <66 Years | | | ≥66 Years | | |
| Liability Class | pp | Pp | PP | pp | Pp | PP |
| 1. All women, men age ≤25 years | .000 | .000 | .000 | .000 | .000 | .000 |
| 2. Men age 26–35 years | .001 | .004 | .004 | .001 | .001 | .001 |
| 3. Men age 36–45 years | .001 | .029 | .029 | .001 | .001 | .001 |
| 4. Men age 46–55 years | .001 | .134 | .134 | .001 | .035 | .035 |
| 5. Men age 56–65 years | .001 | .605 | .605 | .001 | .213 | .213 |
| 6. Men age 66–75 years | .001 | .909 | .909 | .001 | .833 | .833 |
| 7. Men age ≥76 years | .025 | .950 | .950 | .025 | .950 | .950 |

Note.—Allele P is associated with hereditary PC. Of the first 143 families (141 of which were genotyped for this study), 13 were initially identified as having a related family member with BC. Therefore, the gene frequency of .003 suggested by Carter et al. (1992) for all hereditary PC was reduced to .00027 (.003 × [13/143]). Men who reported that they had never had a PSA test were coded as unknown. In the 12 families with BC, only cases of PC that were related by blood to the person(s) with BC were considered to be affected, resulting in three cases of PC in these 12 families being coded as unknown. Subjects with BC were coded as affected, with a liability class of 2. Phenocopy rates in the analysis of all 141 families or of families without a family member with BC were as used in the genomic scan; for liability classes 1–7, these rates were .000, .001, .001, .005, .010, .050, and .050, respectively.

for subsequent analyses of a non–age-segregated data set.

Under the hypothesis of a joint PC-BC locus, individuals biologically unrelated to the patient with BC (i.e., those related only by marriage to the patient with BC) would not be expected to show linkage to the same locus as would be expected in patients biologically related to individuals with BC. For this reason, three patients with PC were coded as unknown. Because all coded affected men were biologically related to the patient with BC, a low phenocopy rate of .001 was used for all but the oldest age class among the groups with PC-BC (table 1). A relaxed age-dependent phenocopy rate was used for analyses of families without a family history of BC (table 1). Subjects with BC but without PC were considered affected; however, genotypes were available for only one such person, and genotypes were inferred for another. All three men with PC-BC were genotyped. The age at onset of BC was not included in the mean age-at-onset calculations; only the age at onset of PC was used. Fi-

## Table 2

**Characteristics of 12 Families with PC and a History of BC**

| Category and Family | No. of Cases of PC | Mean Age at Diagnosis of Sampled Patients with PC (years) | No. of Cases of BC | Relationship between Cases of PC and Cases of BC |
|---|---|---|---|---|
| Early-onset PC: | | | | |
| 1 | 4 | 57.3 | 1[a] | Second degree |
| 2 | 5 | 63.5 | 2[a] | First degree |
| 3 | 5 | 64.0 | 1[a] | Second degree |
| 4 | 4 | 65.0 | 1[a] | First degree |
| 5 | 4 | 65.3 | 1[a] | First degree |
| 6 | 4 | 65.3 | 1[a] | First degree |
| Overall | 26 | 63.5 | 7 | First degree (5), second degree (2) |
| Late-onset PC: | | | | |
| 7 | 4 | 66.5 | 1[a] | First degree |
| 8 | 4 | 68.3 | 1 | First degree |
| 9 | 4 | 68.5 | 3[b] | First degree |
| 10 | 3 | 70.3 | 1[a] | First degree |
| 11 | 3 | 71.0 | 1 | First degree |
| 12 | 3 | 72.0 | 1[a] | First degree |
| Overall | 21 | 69.6 | 8 | First degree |

[a] Primary BC confirmed by medical records or death certificate.
[b] Two cases were confirmed by medical records or death certificate.

**Table 3**

**Analysis of Six Families with Early-Onset PC-BC**

| Marker | Distance from Preceding Marker (cM) | Maximum Positive LOD Score ($\theta$) | HLOD ($\theta$; $\alpha$) | $NPL_{pairs}$ ($P$) |
|---|---|---|---|---|
| D1S1160 | ... | .51 (.18) | .62 (.00; .37) | .522 (.284) |
| ATA9B08 | 2.74 | .75 (.16) | .75 (.16; 1.00) | .950 (.172) |
| D1S489 | 6.58 | .44 (.14) | .45 (.08; .77) | 1.177 (.124) |
| D1S1597 | .10 | .83 (.04) | .89 (.00; .76) | 1.351 (.096) |
| D1S434 | .10 | .83 (.00) | .83 (.00; 1.00) | 1.525 (.073) |
| D1S402 | 1.09 | .90 (.14) | .90 (.14; 1.00) | 1.722 (.053) |
| D1S407 | 2.73 | 3.65 (.00) | ...[a] (.00; 1.00) | 1.844 (.043) |
| D1S507 | .10 | 2.81 (.04) | 2.81 (.04; 1.00) | 1.847 (.043) |
| GATA29A05 | 3.30 | 1.65 (.10) | 1.65 (.10; 1.00) | 1.817 (.045) |
| D1S552 | 8.28 | 1.02 (.12) | 1.02 (.12; 1.00) | 1.409 (.088) |

[a] No evidence of heterogeneity was seen.

nally, in all families, men of age ⩾45 years who reported being unaffected but who indicated either that they (1) had not had a prostate-specific antigen (PSA) test during the preceding 5 years, (2) did not know whether they had ever had a PSA test, or (3) had an elevated PSA level but did not have physician-diagnosed benign prostatic hyperplasia were, for purposes of the analyses, coded as unknown.

## Results

### *Analysis of Genomewide Screen*

The first set of 70 families to complete data collection as part of PROGRESS was initially genotyped with 387 markers spanning the genome at an average resolution of 10 cM. The genomewide scan involved a total of 512 genotyped individuals, of whom 247 were affected men. Linkage analysis of these 70 families used a model that was based on age-dependent penetrance values and that closely followed the predictions by Carter et al. (1992). Details of this model have been described elsewhere (McIndoe et al. 1997). Although analysis of this and an expanded data set of ~150 families is still in progress, an initial analysis of these first 70 families, made by GENEHUNTER (Kruglyak et al. 1996), showed several peaks with LOD scores ⩾1.0. In the region described here, we observed a peak multipoint LOD score under the assumption of heterogeneity (HLOD) of 1.65 (proportion of families estimated to be linked [$\alpha$] .435) and an NPL score of 2.13 ($P$ = .02), in the short arm of chromosome 1. This peak was associated with one marker, D1S1597. A two-point analysis with this marker resulted in a maximum HLOD score of 0.89 at $\theta$ = .0 and $\theta$ = .34.

Stratification by age and/or other types of cancer has been a useful method for isolation of homogeneous subsets of families in efforts to map common disease genes such as the *BRCA1* breast-ovarian cancer gene (Hall et al. 1990) and the *BRCA2* breast cancer gene (Wooster et al. 1994). The region defined by D1S1597 at 1p36 is notable because it is associated with LOH in several types of CNS tumors, and prior epidemiological studies have shown a relationship between PC and cancer of the CNS (Carter et al. 1993; Goldgar et al. 1994; Isaacs et al. 1995). Therefore, we stratified our larger data set of 141 families with PC, by mean age at diagnosis of

**Table 4**

**Analysis of Six Families with Late-Onset PC-BC**

| Marker | Distance from Preceding Marker (cM) | Maximum Positive LOD Score ($\theta$) | HLOD ($\theta$; $\alpha$) | $NPL_{pairs}$ ($P$) |
|---|---|---|---|---|
| D1S1160 | ... | .00 (.50) | .00 (.50; 1.00) | −1.520 (.941) |
| ATA9B08 | 2.74 | .00 (.50) | .00 (.50; 1.00) | −1.554 (.941) |
| D1S489 | 6.58 | .41 (.00) | .41 (.00; 1.00) | −.128 (.497) |
| D1S1597 | .10 | .36 (.12) | .36 (.00; .56) | −.397 (.656) |
| D1S434 | .10 | .63 (.00) | .63 (.00; 1.00) | −.394 (.656) |
| D1S402 | 1.09 | .12 (.24) | .12 (.22; .86) | −.420 (.656) |
| D1S407 | 2.73 | .11 (.22) | .11 (.22; 1.00) | −.450 (.673) |
| D1S507 | .10 | .41 (.12) | .41 (.12; 1.00) | −.449 (.673) |
| GATA29A05 | 3.30 | .00 (.50) | .00 (.50; 1.00) | −.471 (.673) |
| D1S552 | 8.28 | .00 (.50) | .00 (.50; 1.00) | −.468 (.726) |

**Table 5**

**LOD and NPL Scores at D1S407, for 12 Families with PC-BC**

| Category and Family | Mean Age at Diagnosis of Sampled Patients with PC (years) | LOD Score at $\theta = 0$ | $NPL_{pairs}$ Score ($P$) |
|---|---|---|---|
| Early-onset PC: | | | |
| 1 | 57.3 | .49 | −.408 (.344) |
| 2 | 63.5 | .86 | 1.342 (.121) |
| 3 | 64.0 | .04 | .001 (.422) |
| 4 | 65.0 | .32 | 1.463 (.156) |
| 5 | 65.3 | .46 | .816 (.438) |
| 6 | 65.3 | 1.49 | 1.301 (.156) |
| Overall | 63.5 | 3.65 | 1.844 (.043) |
| Late-onset PC: | | | |
| 7 | 66.5 | .30 | .000 (.750) |
| 8 | 68.3 | −.13 | −.805 (.438) |
| 9 | 68.5 | −1.68 | −1.114 (.813) |
| 10 | 70.3 | −1.09 | −.816 (1.000) |
| 11 | 71.0 | .52 | .816 (.438) |
| 12 | 72.0 | .24 | .816 (.438) |
| Overall | 69.6 | −1.84 | −.450 (.673) |

PC and the presence or absence of a family history of primary BC. When the mean age at diagnosis among sampled affected men was <66 years, families were considered "early onset"; families in which the mean age of diagnosis among sampled affected men was ⩾66 years were considered "late onset."

### *Families with PC-BC*

Among the first 141 PROGRESS families, 38 were identified in which one or more family members described a family history of BC in an individual(s) related by blood to the patient with PC. Because the brain is a frequent site of metastasis (Ruddon et al. 1981), and because the accuracy of familial cancer reporting is highest among first-degree relatives (Love et al. 1985; Airewele et al. 1998), only those cases of BC that were either confirmed by medical records or death certificates or reported by two or more first-degree relatives were included in the analysis, which reduced the data set to 12 families. Eleven of these families self-identified as white, and one self-identified as nonwhite. For these 12 families, a total of 15 cases of primary BC were reported; these included 9 gliomas, 1 CNS lymphoma, 2 malignant brain tumors with unspecified histological type, and 3 with unknown histology for whom medical records have been requested but not yet received. Twelve (80%) of these 15 cases of BC have been validated by medical records, including three men with PC who subsequently developed primary BC. The CNS lymphoma occurred in a family with a confirmed glioma and did not contribute to the linkage result. The other 26 families initially reporting a member(s) with BC (29 cases) were reclassified as not having invasive brain tumors, on the basis of the following: (1) medical records confirmed another primary site of cancer either with brain metastases (6 cases) or with no mention of BC (8 cases); (2) on subsequent follow-up, the cancers were determined to be nonmalignant brain tumors (3 cases); or (3) cases were not reported by at least two first-degree relatives and have not been confirmed by medical records (12 cases).

Medical records were also requested, to verify the PC diagnoses in these 141 families. To date, we have received medical records for 459 (94.8%) of the 484 sampled affected men; 99.8% verified the self-reported cases of PC.

### *Two-Point Analysis of 12 Families with PC-BC*

The mean age at diagnosis of PC in 141 families was 66.3 years. The 12 families with associated BC (table 2) were separated according to the mean age at diagnosis of PC in the 39 sampled affected men, resulting in 6 families with a history of BC and early-onset (mean age <66 years) PC and 6 families with a history of BC and late-onset (mean age ⩾66 years) PC. The six families with early-onset PC-BC had a total of 26 cases of PC, with 21 of them genotyped. The mean age at diagnosis of PC in genotyped affected men in the families with early-onset PC was 63.5 years. A total of seven cases of BC were reported in these families—five in first-degree relatives of the patients with PC and two in second-degree relatives of the patients with PC. Both of the second-degree relatives with BC are related to the patients with PC through a female relative.

The six families with BC and late-onset PC had 21 family members with PC (18 were genotyped). The mean age at diagnosis of the patients genotyped for PC in these families was 69.6 years (table 2). A total of eight cases of BC were reported in first-degree relatives of these cases, including two men with PC and BC. One family is notable for having three siblings with BC. The remaining 129 families with no confirmed cases of primary BC were also divided by mean age at diagnosis of PC (<66 years, 63 families; and ⩾66 years, 66 families).

The 25-cM region surrounding D1S1597 was analyzed in detail, for linkage at 1p36. Separate transmission models were generated for the linkage analysis of the two age-at-onset groups (table 1). For the six families segregating BC and in which the average age at diagnosis of PC was <66 years, a peak two-point LOD score of 3.65 at $\theta = .00$ was observed, with D1S407 (table 3). This marker is ~4 cM from D1S1597, the marker for which the original LOD score was noted in the genomewide screen. Although the maximum LOD scores were positive across most of the same region for the six families with late-onset BC (table 4), none was >1.0.

Three of these families with late-onset PC did, however, have positive LOD scores and haplotypes consistent with linkage to this region (table 5).

When the 12 families are considered together, analysis of all 12 families gave a peak LOD score of 3.22 at $\theta = .06$, with D1S507, with no significant evidence for heterogeneity. The closest adjacent marker, D1S407, gave a LOD score of 2.57 at $\theta = .06$, which increases to 2.70 at $\theta = .0$ when heterogeneity and $\alpha = .68$ are assumed. Linkage was rejected for the early-onset ($n = 63$) and late-onset ($n = 66$) families that did not have reported or confirmed cases of BC, with LOD scores for D1S407 that were −7.12 and −6.02, respectively, at $\theta = .0$ (table 6). However, positive LOD scores were seen at higher $\theta$ values for the early-diagnosis non–BC group (maximizing at LOD score 0.53; $\theta = .24$), suggesting a subset of linked families. Linkage was similarly negative with marker D1S1597 for all 129 families with PC but without a family history of BC (data not shown). Analysis using HOMOG and marker D1S407 in all 141 families did not detect significant evidence of heterogeneity. However, if one assumes heterogeneity, then $\alpha$ is estimated to be .15 when the model for the 12 families is used. Because most of the 141 families do not have a member with BC, however, the alternate model—that is, that for the families that do not have BC—should be more appropriate; this model, which differs in having higher phenocopy rates, results in an estimate of $\alpha = .37$. The wide range in the estimates of $\alpha$ highlights the latter's sensitivity to the model chosen.

### *Multipoint Analyses*

Multipoint linkage analysis with 10 markers, by GENEHUNTER (Kruglyak et al. 1996), in the six families with BC and early-onset PC yielded a maximum NPL score of 1.85 ($P = .043$) at a point corresponding to the position of D1S507 (table 3). GENEHUNTER does not use the complete information in all pedigrees, and therefore this result may be an under-/overestimate. The peak multipoint 10-marker HLOD score was 0.81 at $\alpha = .72$, at a point between GATA29A05 and D1S552, 6.59 cM away from the NPL peak. Multipoint analysis of the smaller region of interest, including D1S407–D1S552, yielded an NPL score of 2.24 ($P = .020$) and an HLOD of 1.65 at $\alpha = .78$ and a LOD score of 1.48. The significant multipoint NPL score and nonsignificant multipoint parametric-linkage score suggested model misspecification. When, to test the sensitivity to this parameter, the phenocopy rates were relaxed to match those used in the non–BC group, the LOD and HLOD scores both equaled 2.33 ($\alpha = 1$).

The strongest NPL scores were observed for four adjacent markers spanning a 6.1-cM region bounded by D1S402 and GATA29A05, in which four adjacent markers had associated NPL scores with $P$ values of ~.05 (table 3). This is less than might be expected from the positive two-point result over several adjacent markers. However, the NPL score measures only haplotype sharing among affected individuals; thus, linkage information from older unaffected men is not represented. When unaffected men are coded as unknown, the LOD score drops from 3.65 to 2.83; that is, these men contributed to ~33% of the two-point LOD score. NPL scores also may be underestimated in larger families that, because of computational limitations, had informative individuals dropped from analysis by GENEHUNTER.

To determine which set of families was most likely to show linkage to each of the defined loci, the families were specifically examined for possible linkage to the *HPC1* (1q24-25) and *PCAP* (1q42.2-43) regions (Smith et al. 1996; Berthon et al. 1998). Two families (families 8 and 9) had positive LOD scores with marker D1S1589 in the *HPC1* region that were higher than those with marker D1S407, and two families (families 9 and 10) had positive and higher LOD scores with marker D1S2785 in the 1q42.2-43 region. Interestingly, all three were late-onset families (table 7). If these three families are excluded from the data set, analysis of the remaining nine families, with no stratification by mean age at diagnosis of PC, yields a maximum LOD score of 4.74 at ($\theta = .00$), with D1S407, and a maximum $NPL_{pairs}$ score of 2.05 ($P = .027$) at a position corresponding to D1S507 (table 8). The $NPL_{all}$ score for these nine families was 1.57 ($P = .065$). These data suggest that linkage to other defined PC–susceptibility loci, rather than mean

**Table 6**

**LOD Scores with D1S407, for Stratified Subsets of Families with PC**

| Family History of BC and Mean Age at Onset of PC | No. of Families | LOD Score at $\theta$ = | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | .00 | .02 | .04 | .06 | .08 | .10 | .20 | .30 | .40 |
| Present: | | | | | | | | | | |
| <66 years | 6 | 3.65 | 3.46 | 3.28 | 3.09 | 2.90 | 2.71 | 1.77 | .90 | .25 |
| ≥66 years | 6 | −1.84 | −.87 | −.51 | −.30 | −.16 | −.07 | .10 | .08 | .03 |
| Absent: | | | | | | | | | | |
| <66 years | 63 | −7.12 | −4.23 | −2.72 | −1.74 | −1.05 | −.55 | .48 | .44 | .14 |
| ≥66 years | 66 | −6.03 | −4.94 | −4.07 | −3.37 | −2.79 | −2.31 | −.82 | −.22 | −.03 |

**Table 7**

**LOD Scores at Three Putative PC Loci, for 12 Families with PC-BC**

| Family | Maximum Absolute LOD Score with Marker[a] | | |
|---|---|---|---|
| | D1S407 | D1S1589 (*HPC1*) | D1S2785 (*PCAP*) |
| 1 | .49 | −.05 | .03 |
| 2 | .86 | −.24 | .08 |
| 3 | .04 | .031 | −.28 |
| 4 | .32 | .16 | .25 |
| 5 | .46 | .26 | −.84 |
| 6 | 1.49 | −.34 | −.38 |
| 7 | .30 | −.18 | −.89 |
| 8[b] | −.13 | .42 | −.19 |
| 9[b] | −1.68 | .28 | .50 |
| 10[b] | −1.09 | −.09 | .22 |
| 11 | .52 | .46 | −.28 |
| 12 | .24 | −.10 | .14 |

[a] All LOD scores shown were maximal at $\theta = 0$, except for that for D1S1589 in family 3 (underlined), where $\theta = .08$.
[b] Showed stronger evidence of linkage at other defined loci.

age at diagnosis, may account for the locus heterogeneity observed even in this highly stratified subset of families.

### *Haplotype Analysis*

Haplotypes for all 12 families are shown infigure 1. Haplotype sharing is noted among all or nearly all affected men in families 2, 4–7, 11, and 12. Families 8–10 had better evidence of linkage to other loci. Note that three of the remaining families have a later average age at onset. It is possible that some families in which all affected men do not share a haplotype, such as family 3, nevertheless contain individuals who share a mutation at this locus, and an occasional individual not sharing a haplotype may simply reflect sporadic disease. We note that family 9 has three cases of BC. Interestingly, this family showed little sharing of haplotypes and a strongly negative LOD score with D1S407 (fig. 1and table 5). Given the infrequency of BC in the families with evidence of 1p36 linkage, a high frequency of BC in one family may suggest a separate genetic risk.

## Discussion

We have identified by linkage analysis a chromosome 1p36 region that may contain a hereditary PC locus. Susceptibility to common diseases such as PC is expected to be genetically heterogeneous. The putative PC–susceptibility locus that the present study has identified at 1p36, together with those previously reported at 1q24-25 (Smith et al. 1996), 1q42.2-43 (Berthon et al. 1998), and the X chromosome (Xu et al. 1998), suggest that this is the case in PC. Our data indicate further that the locus at 1p36 is most strongly associated with familial PC in kindreds that also have a history of BC.

Although the overall data set suggests that families with an early age at diagnosis are more likely to show linkage to the 1p36 region, several of the late-onset families suggest linkage to 1p36 as well. Interestingly, the average age of the members of all three families that show more positive LOD scores to either the 1q42-43 or 1q24-25 loci was greater; removal of these three families results in both a significant increase in the LOD score, at 1p36, for the remaining families and some improvement of the overall NPL score, regardless of age at diagnosis. This subset of nine families represents 75% of the families with both a high risk of PC and a family member with BC and represents 100% of those same families in which the mean age at diagnosis of PC is <66 years. Of the 141 families, 6.4% were in this subset. Some families lacking a history of primary BC may show linkage to this locus as well; this could be due to un-

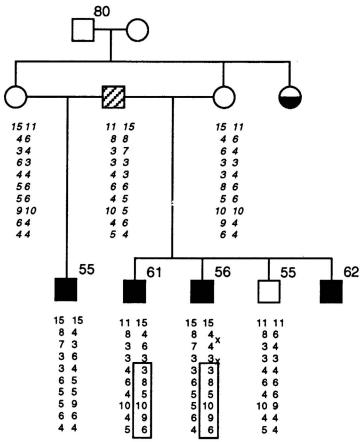
**Table 8**

**Nine Families with PC, Family History of BC, and No Evidence of Linkage to Either *HPC1*(1q24-25) or *PCAP* (1q42-43)**

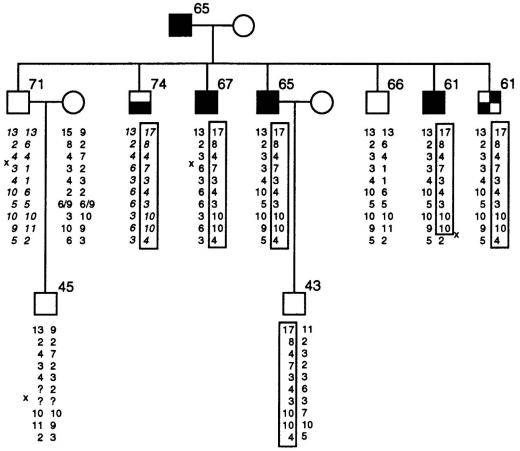
| Marker | Distance from Preceding Marker (cM) | Maximum Positive LOD Score [a]($\theta$) | HLOD ($\theta$; $\alpha$) | $NPL_{pairs}$ ($P$) |
|---|---|---|---|---|
| D1S1160 | ... | .17 (.26) | .31 (.00; .21) | −.100 (.521) |
| ATA9B08 | 2.74 | .46 (.22) | .46 (.22; 1.00) | .277 (.376) |
| D1S489 | 6.58 | .87 (.10) | .89 (.04; .77) | 1.493 (.075) |
| D1S1597 | .10 | 1.85 (.00) | 1.86 (.00; .94) | 1.654 (.057) |
| D1S434 | .10 | 1.64 (.00) | 1.64 (.00; 1.00) | 1.801 (.043) |
| D1S402 | 1.09 | 1.73 (.10) | 1.73 (.10; 1.00) | 1.965 (.032) |
| D1S407 | 2.73 | 4.74 (.00) | ...[b] (.00; 1.00) | 2.050 (.027) |
| D1S507 | .10 | 3.84 (.02) | ...[b] (.02; 1.00) | 2.052 (.027) |
| GATA29A05 | 3.30 | 2.04 (.08) | 2.04 (.08; 1.00) | 2.012 (.029) |
| D1S552 | 8.28 | 1.01 (.14) | 1.01 (.14; 1.00) | 1.541 (.069) |

[a] Calculated by use of the early-onset PC-BC model.
[b] No evidence of heterogeneity was seen.

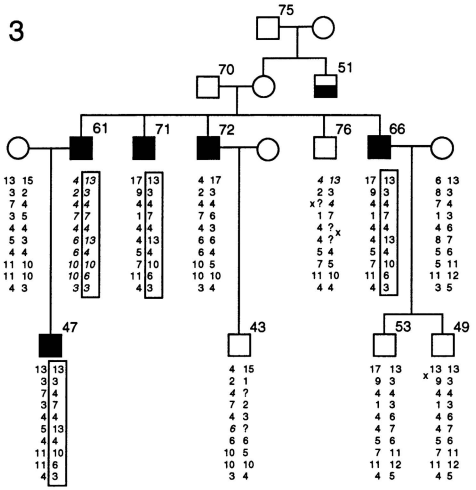
1



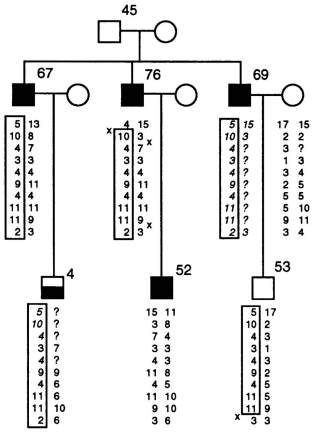
2



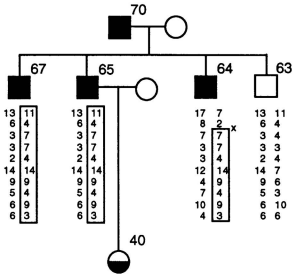
3



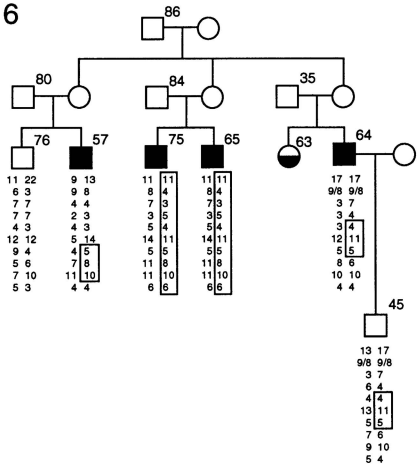
4



5



6



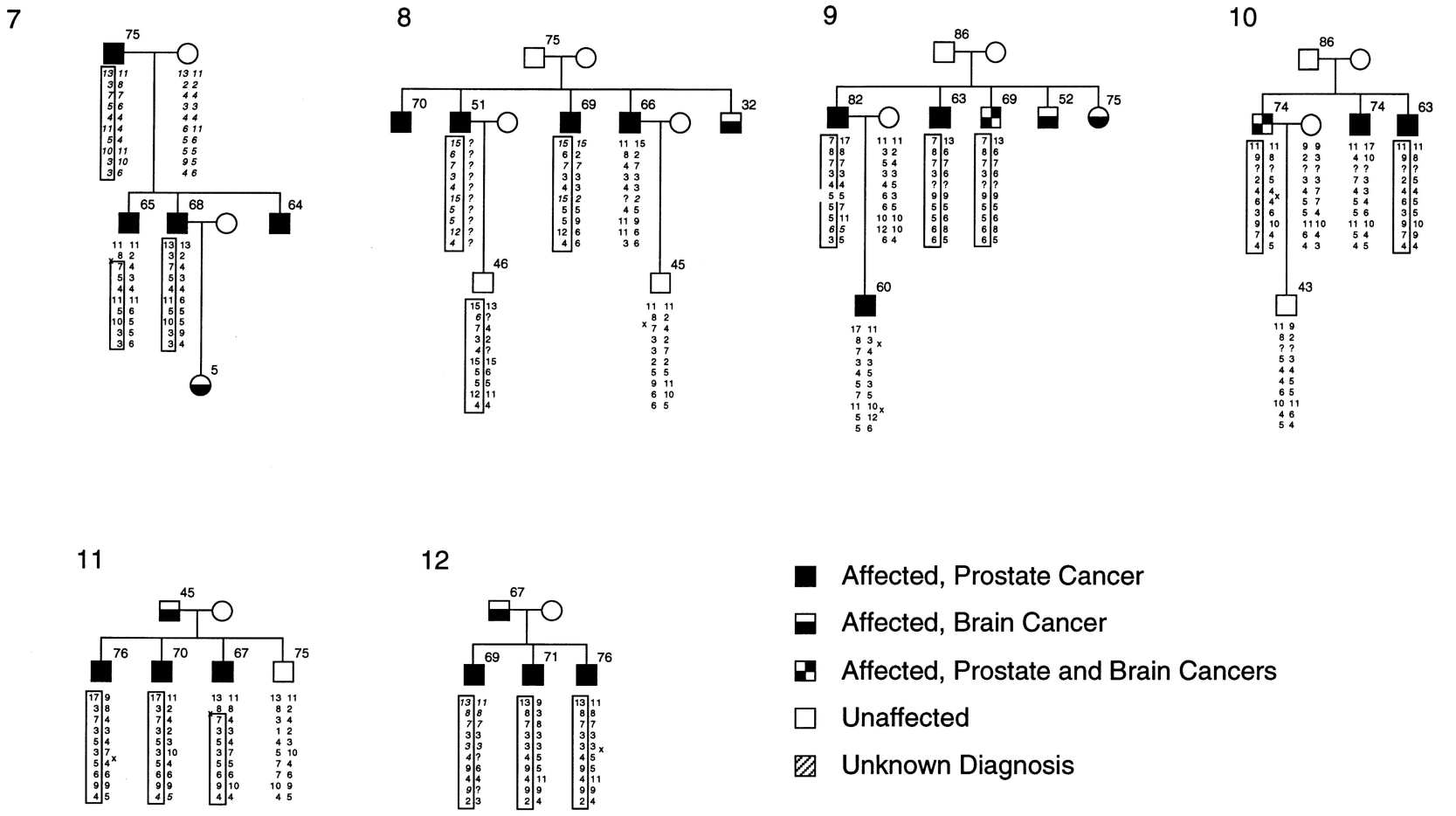



**Figure 1** Haplotypes for 12 families. The order of markers is as listed in table 3. Inferred genotypes are italicized. The haplotype or haplotype segment most commonly shared by affected pedigree members is outlined in men with known diagnoses. The age at diagnosis is given for affected individuals, whereas the age at sampling is given for unaffected men. To obscure the identity of the pedigrees, pedigree members with uninformative diagnoses and many sisters of affected men have been omitted, except when it they have been necessary to show relationships; these omissions include 39 genotyped individuals whose information was used to assist in haplotype construction. Also to obscure the identity of the pedigrees, vital status is not shown. X = point of likely recombination.

derreporting of BC by families, the inability to confirm all cases of BC in the data set, or this allele's weaker penetrance for BC compared with PC.

The lack of statistical significance of the multipoint parametric-linkage result may be due to model misspecification. This explanation is consistent with (1) the significance of the $NPL_{pairs}$ score at the .05 level; (2) the 6.59-cM difference, in the peak multipoint score, between the 10-point LOD score and the NPL score; and (3) the improved LOD score when the sporadic rate is relaxed. The significant two-point LOD score is unlikely to be a false-positive result in the face of (*a*) positive two-point LOD scores at multiple informative markers over a 25-cM region (table 3) and (*b*) significant evidence of haplotype sharing among affected men in the NPL analysis. One cause of false-positive two-point LOD scores is chance sharing of a rare or underestimated allele at a marker. However, the families contributing to the evidence of linkage here share different alleles at most of the multiple markers suggesting linkage. In addition, sharing of haplotypes would be inconsistent with a false-positive two-point result based on the sharing of rare marker alleles. Whereas two-point analysis relies on the same model, it is known to be more robust to model misspecification and locus heterogeneity than is multipoint analysis (Risch and Giuffra 1992). In addition to the inheritance pattern, areas that may contribute to model misspecification include the sporadic rate, the age-at-diagnosis penetrance functions, the disease-allele and marker frequencies, and the map distances. In addition, the multipoint HLODs are higher than the LODs, suggesting that locus heterogeneity is affecting the power to detect linkage.

We note that 14% (6/44) of the reported cases of BC in our data set were found, by review of medical records, to be metastases from other primary sites and that 18% (8/44) were confirmed as other primary sites, with no mention of BC in the medical or death records. Thus, careful confirmation of BC phenotypic information will be critical for follow-up studies.

We did not observe significant evidence for chromosome 1p36 linkage in the early- or late-onset families that did not report a family history of primary BC. Thus, there is not strong evidence to suggest that this chromosomal region accounts for a significant portion of hereditary PC in a family classically defined as "high risk." Some families without reported cases of BC may be linked, however; identification of such families will be difficult and likely will require characterization of an actual disease gene.

We have compared the distribution of other types of cancer—including colon, bladder, kidney, lung, pancreatic, breast, and ovarian cancer (the latter two in first-degree relatives only)—in the 12 families with PC-BC versus the 129 families without PC-BC, to determine whether the families with PC-BC have a higher frequency of other types of cancer. The cancer cases that were considered were those which had been reported by two or more male blood relatives. No significant differences were observed (in all comparisons, $P > .1$ by Fisher's exact test).

All of the families with a confirmed tissue type had at least one member with a neuroepithelial malignancy. The majority of families in this data set had a family history of glioma. The 1p36 region has been implicated in multiple types of BC, including neuroblastomas (Maris et al. 1995; Martinsson et al. 1995; Van Roy et al. 1997), glioblastomas (Bello et al. 1995*a*), meningiomas (Bello et al. 1994*a*), oligodendrogliomas (Bello et al. 1995*b;* Kraus et al. 1995), astrocytomas, and mixed oligoastrocytomas (Ransom et al. 1992; Kraus et al. 1995). Stratification either by tumor type or by age at either diagnosis of BC or death, however, did not show subsets of families that were more or less likely to be linked. Stratification by family history of cancers at other sites has not yet been done in the larger data set of 141 families, but there appears to be no obvious excess of other tumor types in these 12 families.

The 1p36 region defined by D1S407 lies proximal to the consensus deletion region in neuroblastomas, which includes the *p73* gene (Kaghad et al. 1997). Should this linkage be confirmed in additional data sets, candidate genes that localize to this region would encompass the *FGR* oncogene and four genes—*TNFR2, DAN, ID3* (*heir1*), and *CDC2L1*(*p58*)—excluded as the neuroblastoma tumor-suppressor gene (White et al. 1995).

Although epidemiological data have suggested a possible familial association between PC and BC (Carter et al. 1993; Goldgar et al. 1994; Isaacs et al. 1995), we are not aware of any previous reports of a genetic link between PC and BC. PC is not known to be associated with familial cancer syndromes with associated brain malignancies such as von Hippel–Lindau or neurofibromatosis, and its primary metastatic site is bone (Ruddon 1981). One possible explanation for the genetic association observed here, therefore, is that there is at 1p36 a gene that functions as a type of general tumor suppressor. Although its primary function is suppression of PC, either weak penetrance of some mutations or certain genetic backgrounds might lead to an increased incidence of other types of cancer, such as BC. If so, our data, which, admittedly, have been ascertained for PC, suggest that mutants in the gene at 1p36 might be highly penetrant for PC but weakly penetrant for BC. A similar situation might account for the rare but statistically significant frequency of cases of male breast cancer and cases of colon cancer in families at high risk for breast cancer, in which the disease is due to inherited mutations in *BRCA2* (Wooster et al. 1994). The increased frequency of ovarian, prostate, and colon cancers in

*BRCA1*-linked families may also be the result of alleles that are weakly penetrant for susceptibility at those sites or in particular backgrounds (Ford et al. 1994). In addition, environmental exposures and epigenetic phenomena may play a role in the frequency of CNS tumors or brain tumors that are due to mutations in this putative locus.

The association of brain tumors with LOH at 1p36, together with a consideration that this locus may contain a primary PC–susceptibility gene, may provide some insight into the type of gene potentially responsible for this PC-BC relationship. Clearly, establishment of a PC–susceptibility gene at 1p36 awaits confirmation through analysis of other, similar data sets. If this is confirmed, we suggest the designation "*CAPB*," for its association with PC-BC. Should confirmation occur, identification of the relevant gene should provide further insight into both the problem of PC etiology and tumor suppressors in general.

## Acknowledgments

We are grateful for the cooperation of and time contributed by the men with PC and by their family members, who are participating in PROGRESS. We thank Michael Brannan and Laurie Hunter for their help with data collection, and we thank Neil Weigand for technical assistance. We thank Drs. Ellen Wijsman and Leonid Kruglyak and members of the CaP CURE Prostate Cancer Consortium for their advice. We also thank Deborah Banker for her insights on chromosome 1. This work was supported by awards from the CaP CURE Foundation (to J.L.S., L.H., G.P.J., and E.A.O.), National Institutes of Health supplement RO1CA56678 (to J.L.S.), American Cancer Society Junior Faculty Award JFRA-558 (to E.A.O.), and an award from the Markey Molecular Genetics Center (to G.P.J.). Finally, we thank the Fred Hutchinson Cancer Research Center for continued support.

## References

Airewele G, Adatto P, Cunningham J, Mastromarino C, Spencer C, Sharp M, Sigurdson A, et al (1998) Family history of cancer in patients with glioma: a validation study of accuracy. J Natl Cancer Inst 90:543–544

Bello MJ, de Campos JM, Kusak EM, Vaquero J, Sarasa JL, Pestana A, Rey JA (1994*a*) Allelic loss at 1p is associated with tumor progression of meningiomas. Genes Chromosomes Cancer 9:296–298

Bello MJ, Leone PE, Nebreda P, de Campos JM, Kusak ME, Vaquero J, Sarasa JL, et al (1995*a*) Allelic status of chromosome 1 in neoplasms of the nervous system. Cancer Genet Cytogenet 83:160–164

Bello MJ, Leone PE, Vaquero J, de Campos JM, Kusak ME, Sarasa JL, Pestana A, et al (1995*b*) Allelic loss at 1p and 19q frequently occurs in association and may represent early oncogenic events in oligodendroglial tumors. Int J Cancer 64:207–210

Bello MJ, Vaquero J, de Campos JM, Kusak ME, Sarasa JL, Saez-Castresana JL, Pestana A, et al (1994*b*) Molecular analysis of chromosome 1 abnormalities in human gliomas reveals frequent loss of 1p in oligodendroglial tumors. Int J Cancer 57:172–175

Berthon P, Valeri A, Cohen-Akenine A, Drelon E, Paiss T, Wöhr G, Latil A, et al (1998) Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. Am J Hum Genet 62:1416–1424

Bova GS, Carter BS, Bussemakers MJG, Emi M, Fujiwara Y, Kyprianou N, Jacobs SC, et al (1993) Homozygous deletion and frequent allelic loss of chromosome 8p22 loci in human prostate cancer. Cancer Res 53:3869–3873

Cannon-Albright L, Eeles R (1995) Progress in prostate cancer. Nat Genet 9:336–338

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC (1992) Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 89:3367–3371

Carter BS, Bova S, Beaty TH, Steinberg GD, Childs B, Isaacs WB, Walsh PC (1993) Hereditary prostate cancer: epidemiologic and clinical features. J Urol 150:797–802

Cher ML, Bova GS, Moore DH, Small EJ, Carroll PR, Pin SS, Epstein JI, et al (1996) Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization and allelotyping. Cancer Res 56:3091–3102

Cooney KA, McCarthy JD, Lange E, Huang L, Miesfeldt S, Montie JE, Osterling JE, et al (1997) Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. J Natl Cancer Inst 89:955–959

Eeles RA, Durocher F, Edwards S, Teare D, Badzioch M, Hamoudi R, Gill S, et al (1998) Linkage analysis of chromosome 1q markers in 136 prostate cancer families. Am J Hum Genet 62:653–658

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, Breast Cancer Linkage Consortium (1994) Risks of cancer in *BRCA1*-mutation carriers. Lancet 343:692–695

Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH (1994) Systematic population-based assessment of cancer risk in first degree relatives of cancer probands. J Natl Cancer Inst 86:1600–1607

Grönberg H, Damber L, Damber J-E, Iselius L (1997*a*) Segregation analysis of prostate cancer in Sweden: support for dominant inheritance. Am J Epidemiol 146:552–557

Grönberg H, Xu J, Smith JR, Carpten JD, Isaacs SD, Freije D, Bova GS, et al (1997*b*) Early age at diagnosis in families providing evidence of linkage to the hereditary prostate cancer locus (HPC1) on chromosome 1. Cancer Res 57: 4707–4709

Grönberg H, Isaacs SD, Smith JR, Carpten JD, Bova GS, Freije D, Xu J, et al (1997*c*) Characteristics of prostate cancer in families potentially linked to the hereditary prostate cancer 1 (*HPC1*) locus. JAMA 278:1251–1255

Hall JM, Lee MK, Morrow J, Newman B, Anderson L, Huey B, King MC (1990) Linkage of early onset familial breast cancer to chromosome 17q21. Science 250:1684–1689

Hayes RB, Liff JM, Pottern LM, Greenberg RS, Schoenberg JB, Schwartz AG, Swanson GM, et al (1995) Prostate cancer risk in US blacks and whites with a family history of cancer. Int J Cancer 60:361–364

Hsieh C-L, Oakley-Garvan I, Gallagher RP, Wu AH, Kolonel

LN, The C-Z, Halpern H, et al (1997) Re: prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. J Natl Cancer Inst 89:1893–1894

Isaacs SD, Kiemeney LALM, Baffoe-Bonnie A, Beaty TH, Walsh PC (1995) Risk of cancer in relatives of prostate cancer probands. J Natl Cancer Inst 87:991–996

Kaghad M, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, Minty A, et al (1997) Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers. Cell 90:809–819

Kraus JA, Koopmann J, Kaskel P, Maintz D, Brandner S, Schramm J, Louis DN, et al (1995) Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. J Neuropathol Exp Neurol 54:91–95

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Landis SH, Murray T, Bolden S, Wingo PA (1998) Cancer statistics, 1998. CA Cancer J Clin 48:6–29

Laniado ME (1998) Prostate cancer potentially linked to the *HPC1* gene. JAMA 279:507

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Love RR, Evans AM, Josten DM (1985) The accuracy of patient reports of a family history of cancer. J Chronic Dis 38: 289–293

Maris JM, White PS, Beltinger CP, Sulman EP, Castleberry RP, Shuster JJ, Look AT, et al (1995) Significance of chromosome 1p loss of heterozygosity in neuroblastoma. Cancer Res 55: 4664–4669

Martinsson T, Sjoberg RM, Hedborg F, Kogner P (1995) Deletion of chromosome 1p loci and microsatellite instability in neuroblastomas analyzed with short-tandem repeat polymorphisms. Cancer Res 55:5681–5686

Massenkeil G, Oberhuber H, Hailemariam S, Sulser T, Diener PA, Bannwart F, Schafer R, et al (1994) P53 mutations and loss of heterozygosity on chromosomes 8p, 16q, 17p, and 18q are confined to advanced prostate cancer. Anticancer Res 14:2785–2790

McIndoe RA, Stanford JL, Gibbs M, Jarvik GP, Brandzel S, Neal CL, Li S, et al (1997) Linkage analysis of 49 high-risk families does not support a common familial prostate cancer–susceptibility gene at 1q24-25. Am J Hum Genet 61: 347–353

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Ransom DT, Ritland SR, Moertel CA, Dahl RJ, O'Fallon JR, Scheithauer BW, Kimmel DW, et al (1992) Correlation of cytogenetic analysis and loss of heterozygosity studies in human diffuse astrocytomas and mixed oligo-astrocytomas. Genes Chromosomes Cancer 5:357–374

Risch N, Giuffra L (1992) Model misspecification and multipoint linkage analysis. Hum Hered 42:77–92

Ruddon RW (1981) Cancer biology. Oxford University Press, New York

Schaid DJ, McDonnell SK, Blute ML, Thibodeau SN (1998) Evidence for autosomal dominant inheritance of prostate cancer. Am J Hum Genet 62:1425–1438

Schleiermacher G, Peter M, Michon J, Hugot JP, Vielh P, Zucker JM, Magdelenat H, et al (1994) Two distinct deleted regions on the short arm of chromosome 1 in neuroblastoma. Genes Chromosomes Cancer 10:275–281

Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, et al (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 274:1371–1374

Stanford JL, Stephenson RA, Coyle LM, Cerhan J, Correa R, Eley JW, Gilliland F, et al. Prostate cancer trends 1973–1995. SEER Program, National Cancer Institute, NCI publ. Bethesda (in press)

Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC (1990) Family history and the risk of prostate cancer. Prostate 17: 337–347

Van Roy N, Jauch A, Van Gele M, Laureys G, Versteeg R, De Paepe A, Cremer T, et al (1997) Comparative genomic hybridization analysis of human neuroblastomas: detection of distal 1p deletions and further molecular genetic characterization of neuroblastoma cell lines. Cancer Genet Cytogenet 97:135–142

White PS, Maris JM, Beltinger C, Sulman E, Marshall HN, Fujimori M, Kaufman BA, et al (1995) A region of consistent deletion in neuroblastoma maps within human chromosome 1p36.2-36.3. Proc Natl Acad Sci USA 92:5520–5524

Whittemore AS, Wu AH, Kolonel LN, John EM, Gallagher RP, Howe GR, West DW, et al (1995) Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. Am J Epidemiol 141:732–740

Williams BJ, Jones E, Zhu XL, Steele MR, Stephenson RA, Rohr LR, Brothman AR (1996) Evidence for a tumor suppressor gene distal to *BRCA1* in prostate cancer. J Urol 155: 720–725

Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, et al (1994) Localization of a breast cancer susceptibility gene, *BRCA2,* to chromosome 13q12-13. Science 265:2088–2090

Xu JF, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, Ewing C, et al (1998) Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat Genet 20: 175–179