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Epidemiology of Hereditary Prostate Cancer: Genetic Analysis of Susceptibility Loci Incorporating Clinical Characteristics

by

Ellen Lee Goode

A dissertation submitted in partial fulfillment of the requirements for the degree of

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Abstract

Epidemiology of Hereditary Prostate Cancer: Genetic Analysis of Susceptibility Loci Incorporating Clinical Characteristics

by Ellen L. Goode

Chairperson of the Supervisory Committee

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Hereditary prostate cancer is a heterogeneous complex disease with at least 5 putative susceptibility loci identified to date: *HPC1* (1q24-25), *PCaP* (1q42.2-43), *HPCX* (Xq27-28), *CAPB* (1p36), and *HPC20* (20q13). Confirmation of linkage in independent datasets is essential to understanding the significance of these findings. Two analyses of high-risk prostate cancer families with 3 or more affected men were conducted using LINKAGE, HOMOG, and GENEHUNTER. First, an analysis of 150 families (2,176 individuals) for linkage to *HPC1* was performed. This dataset includes 640 affected men with an average age at prostate cancer diagnosis of 66.8 years (range 39 – 94). Linkage to multiple 1q24-25 markers was strongly rejected for the sample as a whole. Assuming heterogeneity, however, the estimated proportion of families linked in the entire dataset was 2.6%, using multipoint analysis. Families were stratified by race, mean age at diagnosis, and number of affected men; no significant evidence for linkage was observed. These results indicate that the overall portion of hereditary prostate cancer families whose disease is due to inherited variation in *HPC1* may be less than 34 percent, as originally estimated. Second, clinical data from the medical records of 505 affected men was incorporated into analysis of multiple markers at *HPC1*, *PCaP*, *HPCX*, and *CAPB* in 149

families. Overall, maximum 2-point lods were: 0.43 (θ=0.24) at *HPC1* (D1S1660), 0.57 (θ=0.26) at *PCaP* (D1S2785), 0.16 (θ=0.34) at *HPCX* (DXS984), and 0.86 (θ=0.18) at *CAPB* (D1S407). Distributions of prostate cancer grade and stage and median age at diagnosis were used to stratify families, in addition to race and lod scores at other loci. Analysis of 16 white families with at least one high-grade case and with minimal evidence for linkage to other loci produced a peak NPL score at of 2.03 ($p = 0.03$) at *HPC1* (D1S2818). A maximum NPL of 1.83 ($p=0.04$) was seen at *CAPB* (D1S407) for 37 white families with at least one high-grade cancer suggesting that *CAPB* may be involved with high-grade prostate cancer. Considering clinical data as well as evidence for linkage to other loci may prove useful in understanding multiple loci responsible for hereditary prostate cancer.

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I would like to thank the group of investigators I have had the pleasure of working with and learning from, and I thank David Rider for the unbelievable amount of support he has given me.

DEDICATION

This work is dedicated to my mother, Jane Phillips Goode (1938-1999), who taught me to reach for the stars while keeping my feet on the ground.

CHAPTER 1 LINKAGE ANALYSIS OF 150 HIGH-RISK PROSTATE CANCER FAMILIES AT 1Q24-25 *

Introduction

Prostate cancer is a significant cause of morbidity and mortality. In 2000, there will be an estimated 180,400 new prostate cancer cases in the U.S. and 31,900 deaths due to the disease (Greenlee, et al., 2000). The incidence of prostate cancer varies with age and race. Prostate cancer incidence increases with age; over 75% of all cases are diagnosed in men over age 65 years (American Cancer Society, 1999). African-American men have the highest rate of prostate cancer in the world (American Cancer Society, 1999).

Numerous types of studies support the existence of a genetic component to prostate cancer susceptibility. Migrant studies, for instance, have indicated that genetic factors, in addition to environmental factors, contribute to prostate cancer risk. These studies demonstrated decreased standardized morbidity ratios for prostate cancer among foreign-born compared to native-born U.S. males ranging from 89:100 to 40:100 (Haenszel, 1961; Staszewski and Haenszel, 1965; Haenszel and Kurihara, 1968; Wynder, et al., 1971). Twin studies also suggest that genetics plays a role in prostate cancer risk;

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higher concordance rates were found for prostate cancer in monozygotic twins (19% - 27%) than dizygotic twins (4% - 7%) (Grönberg, 1994; Page, et al., 1997). Case-control and cohort studies of familial aggregation show that prostate cancer tends to cluster in families and have suggested 2- to 3-fold increased risks among first-degree relatives of prostate cancer patients (Fincham, et al., 1990; Spitz, et al., 1991; Whittemore, et al., 1995; Grönberg, et al., 1996). Furthermore, significant relative risks have been observed as high as 5.97 for men with a brother affected at less than 65 years of age (Cannon, et al., 1982) and 10.9 for men with three or more affected first degree relatives (Steinberg, et al., 1990). Some studies have also shown that risk of prostate cancer is increased more in men with affected brothers than in men with affected fathers, consistent with X-linked or autosomal recessive mode of inheritance, as well as a shared childhood environment (Hayes, et al., 1995; Monroe, et al., 1995; Whittemore, et al., 1995). These studies provide the framework for further investigations of inherited prostate cancer susceptibility.

Complex Segregation Analyses

Several complex segregation analyses (CSAs) have been performed to assess whether the observed familial clustering of prostate cancer was consistent with Mendelian inheritance. Each of these CSAs supported the existence of an autosomal dominant prostate cancer susceptibility locus. CSA does not distinguish between one or several loci with similar effects, thus, the existence of more than one autosomal dominant

prostate cancer susceptibility locus is compatible with the CSA results. Carter et al. studied 691 families ascertained through consecutive prostatectomy patients at Johns Hopkins University (Carter, et al., 1992). Results of this study showed evidence for the dominant transmission of a rare (q=0.003) high-risk allele with estimated cumulative risk of prostate cancer for carriers of 88% by age 85 years (Carter, et al., 1992). A more recent CSA was performed on a population-based sample of 2,857 nuclear families ascertained through cases in the Swedish Cancer Register who had sons currently living in Sweden (Grönberg, et al., 1997a). Though it may be important that a general model was not tested (Jarvik, 1998), a dominant model provided the best fit of all major gene models (Grönberg, et al., 1997a). It was estimated that a high-risk allele with a high population frequency (q=0.0167) was responsible for 23% of prostate cancers among carriers by age 65 years and 63% of prostate cancers among carriers by age 85 years (Grönberg, et al., 1997a). A third CSA was performed on 4,288 nuclear families ascertained through radical prostatectomy cases at the Mayo Clinic (Schaid, et al., 1998). Support for an autosomal dominant model in this analysis was strongest in families with a proband diagnosed under the age at 60 years (Schaid, et al., 1998). Results suggested that the risk of prostate cancer by age 85 years was 89% for carriers of a rare high-risk allele (q = 0.006) and 3% for non-carriers of the allele (Schaid, et al., 1998). These CSAs highlight characteristics of families useful for linkage studies: families with multiple affected members and early onset of disease are more likely to segregate a single highly penetrant prostate cancer susceptibility gene (Carter, et al., 1992; Grönberg, et al., 1997a; Schaid, et al., 1998).

Linkage Analyses

The first significant prostate cancer linkage analysis published utilized 91 high-risk prostate cancer families from the U.S. and Sweden (Smith, et al., 1996). This report suggested that a dominantly-inherited prostate cancer susceptibility locus (*HPC1*) in the chromosome 1q24-25 region was responsible for 34% of inherited prostate cancer in families studied. Initially, the authors analyzed a set of 66 North American prostate cancer families and observed a lod score of 2.75 with marker D1S218. When an additional 25 Swedish families were added to the analysis, significant evidence for linkage was provided by a lod score of 3.65 at a recombination fraction (θ) = 0.18 with marker D1S2883. The region was refined to an approximate 15 cM stretch between D1S2883 and D1S422. A maximum parametric multipoint lod score of 5.43 was obtained with markers D1S2883, D1S158 and D1S422 under the assumption of heterogeneity (α = 0.34) with the postulated locus being close to D1S422 (Smith, et al., 1996). The majority of families evaluated were white, but it was noted that two African-American families contributed 1.4 to the original lod score (Smith, et al., 1996). A second report from the same group reported that analysis of 40 North American families in their dataset with an average age at diagnosis < 65 years yielded a parametric multipoint lod score of 3.96, whereas for 39 North American families with an older average age at diagnosis, this value was -0.84 (Grönberg, et al., 1997c). When restricted to 14 North American families with average age at diagnosis < 60 years, the estimated proportion of families linked was 66%, but decreased to 7% for the families with mean

age at diagnosis equal to 70 years or more (Grönberg, et al., 1997c). A similar age effect was observed in a set of 12 Swedish pedigrees analyzed (Grönberg, et al., 1997c).

Several groups have sought to confirm prostate cancer linkage to 1q24-25 with inconsistent results. Cooney et al. analyzed 20 families with 3 or more affected men in a nuclear family, 2 or more men affected at less than 55 years, or prostate cancer in 3 successive generations (Cooney, et al., 1997). Analysis of six 1q24-25 markers by multipoint non-parametric linkage (NPL) methods yielded a maximum NPL score of 1.72 ($p = 0.045$) at marker D1S466. Analysis of 6 African-American families produced a maximum NPL score of 1.44 ($p=0.08$) at D1S158 (Cooney, et al., 1997). In another study, Hsieh et al. reported that non-parametric multipoint linkage analysis of 46 families with mean age at onset < 67 years yielded a NPL score of 1.83 ($p=0.04$) at D1S452 (Hsieh, et al., 1997).

In contrast, other studies have rejected prostate cancer linkage to 1q24-25. These analyses found two-point lod scores for 1q24-25 markers ranging from –25.11 to –2.49 (McIndoe, et al., 1997; Berthon, et al., 1998; Eeles, et al., 1998). A lod score of –2.0 is considered significant evidence against linkage. We previously analyzed 49 of the currently reported 150 families for ten 1q24-25 markers spanning 37 cM and found that lod scores for all ten markers were less than –2.0 at $\theta = 0$ and remained negative at higher values of θ for most markers (McIndoe, et al., 1997). Eeles et al. analyzed 136 families with 2 or more cases of prostate cancer (Eeles, et al., 1998). No significant evidence for

linkage was observed at any of 6 markers studied, including analysis of 35 families with 4 or more cases (Eeles, et al., 1998). Assuming heterogeneity, it was estimated that 4% of the 136 families were likely to be linked to the *HPC1* region. Finally, Berthon et al. studied 47 families with a mean of 3.3 affected men per family and observed significantly negative two-point parametric lod scores for three 1q24-25 markers (Berthon, et al., 1998). Subsequently, evidence for 4 other putative prostate cancer loci have observed: *PCaP* at 1q42.2-43 (Berthon, et al., 1998), *HPCX* at Xq27-28 (Xu, et al., 1998), *CAPB* at 1p36 for which evidence is observed in prostate cancer families with a history of primary brain cancer (Gibbs, et al., 1999b), and *HPC20* at 20q13 (Berry, et al., 2000b). Clearly, estimation of the true proportion of high-risk prostate cancer families linked to 1q24-25 will require more detailed analysis in a large number of families, and consideration of families potentially linked at other loci. Here, we evaluate 150 families with 3 or more affected men for evidence of linkage to the *HPC1* locus using parametric two-point and both parametric and non-parametric multipoint methods and sample stratification.

Methods

Study Subjects

Subject recruitment for the Prostate Cancer Genetic Research Study (PROGRESS) began in July, 1995 and is based on the national distribution of a toll-free telephone number encouraging families throughout the country with multiple cases of prostate cancer to call regarding participation in a genetic study. Families of callers are selected if they meet either of the following criteria: 1) three or more first degree

relatives with prostate cancer, 2) prostate cancer in three successive generations, or 3) prostate cancer in two living first degree relatives diagnosed at less than 65 years. Since the reporting of cancer diagnosis by 2nd or 3rd degree relatives has been shown to be unreliable, the pedigrees used in this analysis were reduced so that affected family members who were not sampled (deceased or no contact) and who were more than 1 generation away from a sampled individual were excluded (Steinberg, et al., 1990; Bondy, et al., 1994). Unaffected men aged 45 years or older were coded as having unknown affected status if they indicated on the questionnaire that they had not had a prostate-specific antigen (PSA) test within the last 5 years, if they didn't know if they had had a PSA test, or if they had an elevated or abnormal PSA and did not have physician diagnosed benign prostatic hyperplasia. Samples from 150 families were genotyped at 3 markers in the 1q24-25 region (D1S1589, D1S518, and D1S1660). Samples from a random subset of families were also genotyped at 3 additional markers within the region D1S2883 (128 families), D1S2818 (129 families), and D1S2127 (137 families). These 6 markers are arranged on 1q24-25 as follows: D1S1589--2.84 cM--D1S2883--3.41 cM--D1S2818--2.00 cM--D1S2127--1.89 cM--D1S518--10.25 cM--D1S1660. Markers D1S2883, D1S2818, D1S2127, and D1S518 lie within the region identified by Smith et al. (1996) as likely to contain *HPC1*. Chromosomal locations of all markers analyzed are presented in Appendix B. Additional information about procedures used for recruitment of families, verification of diagnoses, and collection and genotyping of DNA samples is summarized elsewhere (McIndoe, et al., 1997).

Statistical Analyses

The lod score method of two-point parametric linkage analysis used the MLINK component of LINKAGE v.5.1 (Lathrop, et al., 1984) and the ANALYZE software package (Terwilliger, 1996). HOMOG was used to test for locus heterogeneity and perform two-point analysis assuming heterogeneity (Ott, 1991). Two-point analysis was also performed assuming locus heterogeneity. Under this assumption, a proportion (α) of families are assumed to be linked to the locus being investigated, and a proportion ($1-\alpha$) are assumed not to be linked. Lod scores are calculated at incremental values of α, and a lod score assuming heterogeneity (Hlod) represents the maximum lod score obtained over varying values of both α and θ. Estimates of α without the inclusion of confidence contours should not be overinterpreted. Parametric and non-parametric multipoint analyses used GENEHUNTER v1.2 (Kruglyak, et al., 1996). NPL scores derived from non-parametric multipoint analysis represent a measure of haplotype-sharing among affected individuals. Parametric analyses used 3 model files for the autosomal dominant transmission of prostate cancer. Model S1 is described in detail in McIndoe et al. (1997) where it is referred to as the "Seattle" model. Model S1 was used in the analysis of the entire group of 150 families. However, the age-dependent penetrances in Model S1 were replaced by estimates from our data when families were stratified by race and mean age at diagnosis of sampled affected men. Table 1-1 shows the genotype-specific penetrances of the varied models used to analyze white families with mean age at diagnosis ≤ 65 years (Model S2), white families with mean age at diagnosis > 65 years (Model S3), non-white families with mean age at diagnosis ≤ 65 years (Model S4), and

non-white families with mean age at diagnosis > 65 years (Model S5). To eliminate the possibility of false negative findings due to a difference in model specifications, we also used models from other studies that found significant evidence for 1q24-25 linkage. Model A was used in the linkage analysis reported in Smith et al., (1996) and described in reports by McIndoe et al. (1997), where it is referred to as the "Hopkins" model, and Grönberg et al. (1997c). Model B was used and described by Grönberg et al. (1997c). Allele frequencies were determined using all individuals in the dataset (Ott, 1992; Terwilliger and Ott, 1994).

The highest power to detect linkage is achieved when homogeneous subsets of data, with respect to etiologic locus, are considered, regardless of the transmission model expected. Grönberg et al. (1997c) observed that groups of families with younger mean ages of diagnosis had higher lod scores than groups of families with older mean ages of diagnosis. We used the mean age at prostate cancer diagnosis of sampled affected men to stratify families, because the age at diagnosis for those affected men who were able to submit questionnaires and be sampled was expected to be more reliable than age at diagnosis of all affected men. To further increase homogeneity, we also stratified families by race, number of affected individuals, and whether prostate cancer occurred in 2 or more generations. We also conducted the analyses including only families who had lod scores < 0.35 at any θ at markers in the *PCaP* region (D1S2785), *HPCX* region (DXS984, DXS1200, and DXS1193), or *CAPB* region (D1S407). We used the computer program SIMLINK (Boehnke, 1986) to assess the power of this group of 150 families to detect two-point linkage to a marker with polymorphism information content of 0.84

using lod methods, assuming 88% penetrance for carriers of the disease gene and 5% penetrance for non-carriers by age 85 years.

Results

The 150 families in this report included 2,176 individuals with 640 affected men having an average age at prostate cancer diagnosis of 66.8 years (range 39 - 94) (Table 1-2). The families had an average at 4.3 affected men (range 3 - 10) per family, and the mean age at diagnosis per family was 66.7 years (range 52.8 - 78.0). These characteristics of the overall dataset were similar to the 49 families previously analyzed (McIndoe, et al., 1997). Sixty-six white families, 2 African-American families, and 2 Native-American families had mean age at diagnosis of sampled affected men $\leq$ 65 years. Seventy-eight white families, a Japanese family, and a Latino family had mean age at diagnosis of sampled affected men > 65 years.

Sampled affected men were diagnosed with prostate cancer between the years of 1974 and 1997. For 491 (94.4%) of 520 sampled affected men, medical records have been received, and all but one of the medical records confirmed the prostate cancer diagnosis. A total of 1,128 individuals, including 511 affected men were genotyped for at least one 1q24-25 marker. There was an average at 3.4 genotyped affected men (range 2 - 7) per family, and the mean age at diagnosis for genotyped affected men per family was 65.9 years (range 50.8 - 78.0). Fifty-two unaffected men aged 45 years or older were coded as unknown affected status because they did not report a recent normal PSA test (see methods).

Analysis of All Families

Two-point lod scores at D1S1589, D1S2883, D1S2818, D1S2127, D1S518, and D1S1660 for all families analyzed with Models S1, A, and B are presented in Table 1-3. While 150 families were analyzed at D1S1589, D1S518, and D1S1660, 139 were analyzed at D1S2883, D1S2818, and D1S2127. With all 3 models, there was significant evidence against linkage to each 1q24-25 markers. The lod scores at small θ's were consistently below the -2.0 cutoff for evidence against linkage. Lod scores became positive at higher θ's for D1S2883 (lod = 0.02, θ = 0.42), D1S2127 (lod = 0.09, θ = 0.38), and D1S1660 (lod = 0.16, θ = 0.34), using model S1, but remained negative at other markers. Assuming heterogeneity, analysis using HOMOG showed that two-point lod scores increased to 0.03 (θ = 0) with α = 0.04 at D1S2883 and 0.17 (θ = 0) with α = 0.09 at D1S2127 and estimated that α = 0 for the markers. When the 49 families previously analyzed (McIndoe, et al., 1997) were removed from the analysis, the two-point lod scores at θ = 0 were less than -9.40 for all 6 markers, using model S1, and they showed a similar pattern at higher θ's as the total dataset. Simulations estimated an expected lod score of 0.46 at θ = 0 for the 150 families if 34% of families were linked to *HPC1*. Thus, although the power to achieve a lod score of 3.0 is very low, the lod score range of -30.83 to –18.42 is incompatible with linkage at 34% of the sample and provides strong evidence against linkage for this sample. In fact, SIMLINK results indicate that if only 10% of the families were linked, we'd expect positive lod scores at θ = 0.

The families were also analyzed with more specific versions of Model S1 (Table 1-3). When summed, there was again evidence against linkage all 6 markers with two-point lod scores less than - 27.90 at $\theta = 0$ (data not shown). At higher θ's, lod scores became positive for markers D1S2883, D1S2127, and D1S1660, but remained negative for other markers. Figure 1-1 displays the distribution of maximum two-point lod scores at marker D1S518 which lies within the proposed *HPC1* region. Two-point lod scores at this marker ranged from -2.05 to 0.66, and the median lod score was -0.12. While the majority of families have negative lod scores, we note that there are 21 families with lod scores > 0.30.

Multipoint lod score analysis was performed on the total group of families on 6 markers (D1S1589, D1S2883, D1S2818, D1S2127, D1S518, and D1S1660), and results are given in Table 1-4. Eleven families were not genotyped at markers D1S2883, D1S2818, and D1S2127. Using Model S1, parametric multipoint lod scores throughout the region ranged from -43.25 to -29.00 at positions corresponding to markers. Assuming heterogeneity, a maximum Hlod of 0.023 with an α of 0.026 was found at a position corresponding to marker D1S2127; positive Hlods were also seen at D1S2818 and D1S1660. Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

Analysis of Family Subsets Based on Ethnicity, Mean Age at Diagnosis, and Number of Affected Men

The dataset was further restricted to white families and stratified by mean age at diagnosis of sampled affected men and number of affected men ($\leq$ 65 years, $\leq$ 60 years, > 65 years, $\leq$ 65 years with 5 or more affected men, $\leq$ 65 years with prostate cancer in at least 2 generations). Parametric analyses of these groups of families used Models S2 and S3. Tables 5, 6, and 7 describe two-point results for markers D1S1589, D1S518, and D1S1660, respectively for subgroups of families. In each subgroup at all 6 1q24-25 markers, linkage was rejected and lod scores remained negative at higher θ's, except in a few groups of families at certain markers. Table 1-8 shows results of multipoint analysis on subsets of families. Parametric multipoint analysis consistently yielded lod scores of less than –7.45 at positions corresponding to markers. Non-parametric multipoint linkage produced non-significant NPL scores throughout the region in these subgroups.

Analysis of 78 white families with mean age at diagnosis > 65 years produced two-point lod scores less than -8.69 at $\theta = 0$. Positive lod scores were observed at higher θ's with the following maximum lod scores: D1S1589, lod = 0.11, $\theta = 0.36$; D1S2883, lod = 0.45, $\theta = 0.28$; D1S2818, lod = 0.05, $\theta = 0.36$; D1S2127, lod = 0.49, $\theta = 0.28$; D1S518, lod = 0.27, $\theta = 0.32$; and D1S1660, lod = 0.07, $\theta = 0.36$. Assuming heterogeneity, two-point lod scores rose to 0.59 ($\alpha = 0.20$, $\theta = 0$) at D1S2127 and 0.30 ($\alpha = 0.17$, $\theta = 0$) at D1S518. Multipoint results revealed lod scores < - 15.68 at positions corresponding to markers; however, analyses assuming heterogeneity produced positive

Hlods at all markers except D1S1660. A maximum Hlod was observed at marker D1S2127 of 0.370 with an α of 0.123. No NPL scores were significant in this subgroup, however, an NPL score of 1.68 at D1S2127 reached marginal significance ($p = 0.051$), with p-values of 0.10 and 0.11 at surrounding markers. This marginally significant NPL score at D1S2127 is not consistent with parametric multipoint results. This discrepancy may be explained by a) the small NPL p-value may be the result of chance due to multiple comparison; b) model used in parametric analyses may be inappropriate; or c) men who do not have the disease share a haplotype with affected men in these families. Examination of haplotypes of the 9 families with negative multipoint lod scores and positive NPL scores indicate that the latter possibility is likely.

Analysis of 66 white families with mean age at diagnosis ≤ 65 years revealed no evidence for linkage with consistently negative two-point and multipoint lod scores (even assuming heterogeneity) and non-significant NPL scores (Tables 5 – 8). Restricting to 20 white families with mean age at diagnosis ≤ 60 years revealed two-point lod scores less than –2.00 at $\theta = 0$ that remained negative a higher θ's for all markers except D1S2127. At $\theta = 0$, the two-point lod score at D1S2127 was -1.03, and assuming heterogeneity, this lod score rose to 0.05 ($\alpha = 0.19$, $\theta = 0$). Multipoint analysis, however, revealed negative lod scores and Hlods and estimates of $\alpha = 0$ (Table 1-8).

White families with young age at diagnosis were further stratified by number of affected men per family. Analysis of 21 families with mean age at diagnosis ≤ 65 years

and 5 or more affected men revealed no evidence for linkage (Tables 5 - 8). Assuming heterogeneity, however, a two-point lod score of 0.07 ($\alpha = 0.13$, $\theta = 0$) is obtained at DS2883 and a lod score of 0.02 ($\alpha = 0.56$, $\theta = 0.32$) is obtained at DS2818. Multipoint analysis revealed a maximum Hlod of 0.093 with an α of 0.111 at marker D1S2883. Analysis of 43 families with mean age at diagnosis $\leq$ 65 years and prostate cancer in more than one generation also revealed no evidence for linkage. In this group, however, a lod score of 0.49 ($\alpha = 0.21$, $\theta = 0$) is obtained at DS2127 if heterogeneity is assumed. Multipoint analysis revealed a maximum Hlod of 0.031 ($\alpha = 0.032$) at a position corresponding to marker D1S2818 in this group.

We analyzed 6 non-white families at 1q24-25 markers. Three of these families had positive two-point lod scores, including one African-American family with a lod score of 0.34 at marker D1S518 ($\theta = 0$) and positive lod scores at all other markers. Three of the non-white families had negative two-point lod scores at all markers, including a second African-American family.

Analysis of Family Subsets Based on Potential Linkage to Other Loci

In an effort to decrease heterogeneity due to linkage at other loci, 87 families were also genotyped at marker D1S2785 in the *PCaP* region, at markers DXS984, DXS1200, and DXS1193 in the *HPCX* region, and at marker D1S407 in the *CAPB* region. Though a small positive lod score is not conclusive evidence of linkage in a

given family, we excluded 41 families from the *HPC1* analysis that had a lod score > 0.35 at any θ for these markers and 63 families that were not genotyped at all of these markers to exclude families that might possibly be linked to these other loci. Forty-one of these excluded families also had a small positive lod score at D1S518, and the median lod score at D1S518 ($\theta = 0$) for excluded families was -0.06 (range -1.22 to 0.67).

In 46 families with minimal evidence of linkage to *PCaP*, *HPCX*, or *CAPB*, linkage was rejected using models S1, A, and B (Table 1-9). Two-point lod scores at $\theta = 0$ for were less than –2.0 using all models. Using model S1, lod scores remained negative at higher values of θ for markers D1S518 and D1S2883, but became slightly positive for markers D1S1589 and D1S1660 and at D1S2127 peaked to 0.40 at $\theta = 0.24$ and at D1S2818 reached 0.17 at $\theta = 0.28$. When heterogeneity was assumed, a maximum two-point lod score of 0.10 was observed at D1S1589 ($\theta = 0.32$, $\alpha = 0.06$). Multipoint analysis revealed no evidence for linkage. Using Model S1, parametric multipoint lod scores were less than -6.83 at positions corresponding to markers. Assuming heterogeneity, a maximum Hlod of 0.506 with an α of 0.198 was found at a position corresponding to marker D1S2818. Positive Hlods were also seen at markers D1S1589 (Hlod = .325, $\alpha = 0.163$), D1S2883 (Hlod = .429, $\alpha = 0.181$), and D1S2127 (Hlod = .113, $\alpha = 0.099$). Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

White families with minimal evidence for linkage to other loci were stratified based on mean age at diagnosis. Two-point analysis of 24 white families with mean age at diagnosis $\leq$ 65 years yielded lod scores less than - 3.56 at $\theta = 0$ for all markers, using model S2 (Table 1-10). Two-point lod scores reached 0.31 at D1S2818 ($\theta = 0.24$), became slightly positive at D1S1589 (lod = 0.02, $\theta = 0.34$) and D1S2127 (lod = 0.03, $\theta = 0.34$), and remained negative at higher θ's for other markers. When heterogeneity was assumed, HOMOG revealed a lod score of 0.02 at $\theta = 0.32$ with $\alpha = 0.29$ at D1S1589. Parametric multipoint analysis consistently yielded negative lod scores at positions corresponding to markers. Assuming heterogeneity, however, a maximum Hlod of 0.003 with α of 0.027 at a position corresponding to marker D1S2127 in this group. In this group, Hlods at other markers were negative and all NPL scores were non-significant.

Analysis of 9 white families with minimal evidence of linkage to *PCaP*, *HPCX*, or *CAPB* and with mean age at diagnosis $\leq$ 60 years produced significantly negative two-point lod scores (Table 1-10), except at marker D1S2127 (lod = 0.31, $\theta = 0$). When limited to 8 families in this group that were genotyped at all 6 1q24-25 markers, the two-point lod scores at $\theta = 0$ for all 6 markers were -1.38 at D1S1589, -4.45 at D1S2883, -3.20 at D1S2818, 0.31 at D1S2127, -4.55 at D1S518, and -2.20 at D1S1660. The positive lod score at marker D1S2127 peaked at $\theta = 0$; 4 families contributed positive and 4 families contributed negative lod scores. Assuming heterogeneity, the lod score at marker D1S2127 reached 0.32 ($\theta = 0$) with $\alpha = 0.07$. Multipoint analysis, however,

revealed negative parametric lod scores at all markers (even assuming heterogeneity) and non-significant NPL scores.

Twenty-one white families with mean age at diagnosis > 65 years and with minimal evidence of linkage to other loci were genotyped at all 6 1q24-25 makers. Two-point analysis using model S3 yielded negative two-point lod scores at $\theta = 0$ (Table 1-10). Lod scores at D1S1589 and D1S2127 were not less than -2.0 at $\theta = 0$ in this group. Lod scores became positive at higher at θ's at D1S1589 (lod = 0.06, $\theta = 0.34$), D1S2883 (lod = 0.03, $\theta = 0.36$), and D1S2127 (lod = 0.35, $\theta = 0.22$). No evidence for heterogeneity was detected in two-point analysis ($\alpha = 0$ at all markers). Multipoint analysis assuming heterogeneity, however, revealed evidence for heterogeneity at positions corresponding to markers D1S1589 (Hlod = 0.041, $\alpha = 0.117$) and D1S2883 (Hlod = 0.026, $\alpha = 0.092$). Nonetheless, parametric multipoint lod scores were less than -2.97 at all markers and NPL scores were non-significant.

Analyses were also performed on groups of white families with minimal evidence of linkage to other loci based on number of affected men per family. In a group of 8 white families with mean age at diagnosis for sampled affected men $\leq$ 65 years and 5 or more affected men years, linkage could not be rejected D1S1589, D1S2883, or D1S2818, using two-point analysis (Table 1-10). Lod scores became positive at higher θ's at markers D1S1589 (lod = .10 at $\theta = 0.26$), D1S2883 (lod = .03 at $\theta = 0.32$), D1S2127 (lod = .07 at $\theta = 0.3$), and D1S2818 (lod = .40 at $\theta = 0.2$). It is likely that this

group of families has limited power to detect or reject linkage because of the small number of families. Analysis using HOMOG detected no evidence for heterogeneity. Multipoint analysis revealed negative parametric lod scores at all markers (even assuming heterogeneity) and non-significant NPL scores.

Nineteen white families with minimal evidence of linkage to *PCaP*, *HPCX*, or *CAPB*, with mean age at diagnosis $\leq$ 65 years, and with prostate cancer in more than one generation yielded two-point lod scores of less than -2.0 at $\theta = 0$ for all markers (Table 1-10). Lod scores remained negative at higher θ's for D1S1589 and D1S518, but became positive at the other markers Analysis using HOMOG detected no evidence for heterogeneity using two-point analysis. Multipoint analysis revealed parametric lod scores less than -5.38 at all 6 markers; however, assuming heterogeneity, positive Hlods and evidence for heterogeneity were observed at markers D1S1589 (Hlod = .120, α = 0.130), D1S2883 Hlod = 0.190, $\alpha = 0.147$), D1S2818 (Hlod = .074, $\alpha = 0.090$), and D1S2127 (Hlod = .039, $\alpha = 0.070$). Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

Discussion

The original finding of *HPC1* linkage on chromosome 1q24-25 (Smith, et al., 1996) has proven challenging to replicate. Some reports have supported prostate cancer linkage to this region (Cooney, et al., 1997; Grönberg, et al., 1997c; Hsieh, et al., 1997), while others have not (McIndoe, et al., 1997; Berthon, et al., 1998; Eeles, et al., 1998).

No significant evidence for linkage at a prostate cancer susceptibility locus to 1q24-25 was found in this data set. However, if one assumes the existence of the *HPC1* locus, up to 2.6% of these 150 predominantly white families were estimated to be linked. When families potentially linked to other putative prostate cancer loci were removed, up to 18.1% of the 46 remaining predominantly white families were estimated to be linked (up to 6% of the total sample).

Though no subset of families had statistically significant evidence of linkage, evidence of heterogeneity was observed in selected subsets. Assuming heterogeneity among white families, up to 12.3% of families with mean age at diagnosis > 65 years, 11.1% with mean age at diagnosis $\leq$ 65 years and 5 or more affected men, and 3.2% with mean age at diagnosis $\leq$ 65 years and prostate cancer in more than one generation were estimated to be linked to *HPC1*. When families potentially linked to other putative prostate cancer loci were removed and heterogeneity was assumed, up to 11.7% of remaining white families with mean age at diagnosis > 65 years, 2.7% with mean age at diagnosis $\leq$ 65 years, and 14.7% with mean age at diagnosis $\leq$ 65 years and prostate cancer in more than one generation were estimated to be linked.

Discrepancies in linkage study results may be due to false positive evidence of linkage, differences in analytic methods, and differences in study populations or samples. The first explanation is unlikely, given that support for linkage to the *HPC1* region has been suggested in several studies. To address the issue of analytic methods, we have

tested for linkage using the models used by other groups to detect linkage, and we also used methods that were less model-dependent. We still did not detect significant evidence for linkage in this dataset.

Differences in study populations can be harder to assess. The mean ages of onset, family size, and number of persons affected in this study closely resemble that of Smith et al. (1996). However, there may be important measured or unmeasured differences between the samples.

Affected men participating in PROGRESS were diagnosed between 1974 and 1997, and 83% of cases were diagnosed in 1989 or later. Family recruitment by Smith et al. (1996) began in the mid-1980's (Walsh, 1998), prior to commonplace PSA screening. Adoption of PSA screening led to a sharp increase in new diagnoses of preclinical prostate cancer from 1989 to 1992 and to a decrease in the mean age at diagnosis of new cases (Merrill and Brawley OW, 1997). If the proportion of cases detected by PSA screening is increased in our sample, cases with subclinical disease may have a greater representation than in the samples collected earlier. If *HPC1* leads to more aggressive disease it may be less common in our sample and in others with more recent family collections, relative to those studies with longstanding collections.

It has been argued, in fact, that *HPC1* predisposes to advanced prostate cancer (Grönberg, et al., 1997b). Grönberg et al. (1997b) compared age at diagnosis, PSA level,

digital rectal exam status, stage, grade, primary treatment of prostate cancer cases in families "potentially linked" to *HPC1* to families "potentially unlinked" and to cases from the general population. They found that men in "potentially linked" families had lower mean age at diagnosis and more grade 3 cancers than men in "potentially unlinked" families and more stage III or IV cancers than the general population (Grönberg, et al., 1997b). Because of concerns about ascertainment bias, relevance of comparison groups, and lack of evidence for a linear trend, others have argued against these conclusions (Laniado, 1998; Walther, 1998). Nonetheless, date and method of diagnosis, stage at diagnosis, and measures of cancer progression need to be addressed in further studies of high-risk prostate cancer families.

Differences in the racial makeup of the sample may also be a factor in the differences in linkage results. Though the majority of families contributing to the significant lod score reported by Smith et al. (1996) were white, the African-American families studied had a total lod score of 1.4. Two subsequent studies supporting *HPC1* linkage each included 6 African-American families (Cooney, et al., 1997; Hsieh, et al., 1997). The 6 African-American families studied by Cooney et al. (1997) yielded a maximum NPL score of 1.39 ($p = 0.08$). Though Hsieh et al. (1997) report that analysis of 6 African-American families alone yielded insignificant NPL scores, younger-onset African-American families were included in the analysis which produced significant lod scores. In the present study, only two African-American families were analyzed. One of

these had non-significant positive lod scores across the *HPC1* region. We are currently seeking the participation of additional African-American families.

Linkage at 1q24-25 is likely to be much less common across high-risk families than the 34% originally proposed (Smith, et al., 1996). In another study of 136 families (including 76 families with 3 or more affected men), it was estimated that 4% of families were linked, assuming heterogeneity (Eeles, et al., 1998). The latter number is consistent with our results. Until *HPC1* is cloned and sequenced and mutations in high-risk families can be identified, multiple populations of high-risk families must be studied in more detail to assess the role of this locus in hereditary prostate cancer. A combined dataset of 772 families from 9 research groups estimated that 6 percent of families were linked, revealing a peak multipoint Hlod of 1.40 ($p = 0.01$) at D1S212 (Xu, 2000). It is likely that additional prostate cancer susceptibility genes remain to be mapped since the 4 loci reported to date are unlikely to account for more than one-half of the disease in high-risk families studied. Further linkage studies are required to locate additional hereditary prostate cancer loci.

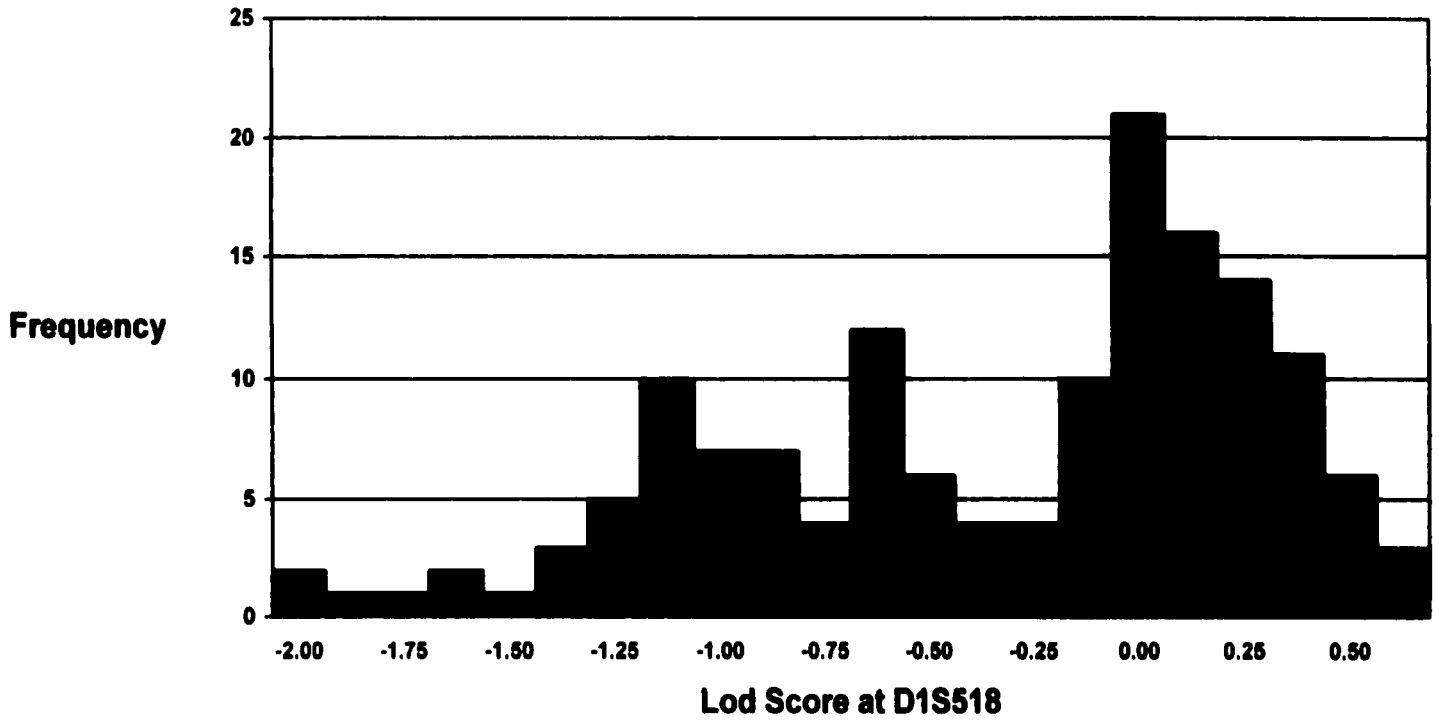

FIGURE 1-1. LOD SCORES AT D1S518 FOR 150 PROSTATE CANCER FAMILIES USING MODELS S2, S3, S4, AND S5. LOD SCORES PLOTTED REPRESENT LOD SCORES WITH THE LARGEST ABSOLUTE VALUE AT ANY Θ.

TABLE 1-1. GENOTYPE SPECIFIC PENETRANCES FOR MODELS S2, S3, S4, AND S5 USED FOR WHITE AND NON-WHITE FAMILIES STRATIFIED BY MEAN AGE AT DIAGNOSIS OF SAMPLED AFFECTED MEN.

		White Families Mean Age at Diagnosis				Non-white Families Mean Age at Diagnosis			
		≤ 65 years Model S2		> 65 years Model S3		≤ 65 years Model S4		> 65 years Model S5	
Liability class		pp*	Pp/PP	pp*	Pp/PP	pp*	Pp/PP	pp*	Pp/PP
1	all women, men aged ≤ 29 years	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	men aged 30 - 39 years	0.001	0.004	0.001	0.000	0.001	0.003	0.001	0.000
3	men aged 40 - 49 years	0.001	0.051	0.001	0.004	0.001	0.046	0.001	0.004
4	men aged 50 - 59 years	0.005	0.286	0.005	0.054	0.005	0.288	0.005	0.053
5	men aged 60 - 69 years	0.010	0.764	0.010	0.430	0.010	0.765	0.010	0.429
6	men aged 70 - 79 years	0.050	0.880	0.050	0.880	0.050	0.880	0.050	0.880
7	men aged 80 years +	0.050	0.880	0.050	0.880	0.050	0.880	0.050	0.880

*Allele P is disease allele with frequency = 0.003.

** Penetrances represent the probability that someone with the given genotype will become affected before or during the age group shown.

TABLE 1-2. CHARACTERISTICS OF 150 PROSTATE CANCER FAMILIES AND SUBSETS BASED ON RACE AND MEAN AGE AT DIAGNOSIS OF SAMPLED AFFECTED MEN.

		White Families Mean Age at Diagnosis		Non-white Families Mean Age at Diagnosis	
	Total Group	≤ 65 years	> 65 years	≤ 65 years	> 65 years
Number of families	150	66	78	4	2
Number of individuals	2,176	922	1,135	96	23
Number of affected men	640	275	330	27	8
Number of genotyped affected men*	511	219	264	21	7
Mean age at diagnosis, yrs. (range)	66.8 (39 - 94)	63.3 (39 - 87)	69.8 (40 - 93)	63.9 (53 - 80)	72.1 (60 - 94)
Mean age at diagnosis for genotyped affected men, yrs. (range)*	65.9 (40 - 87)	62.0 (40 - 82)	69.3 (47 - 87)	63.2 (53 - 80)	69.0 (60 - 74)
Mean number of affected men per family (range)	4.3 (3 – 10)	4.2 (3 - 9)	4.2 (3 - 8)	6.8 (4 – 10)	4.0 (3 - 5)
Mean age at diagnosis of affected men per family, yrs. (range)	66.7 (52.8 - 78.0)	63.0 (52.8 - 70.7)	69.9 (63.4 - 78.0)	62.9 (59.5 - 65.0)	72.0 (71.7 - 72.4)
Mean number of genotyped affected men per family (range)*	3.4 (2 - 7)	3.3 (2 - 5)	3.4 (2 - 5)	5.3 (3 – 8)	3.5 (3 - 4)
Mean age at diagnosis of genotyped affected men per family, yrs. (range)*	65.9 (50.8 - 78.0)	62.0 (50.8 - 66.0)	69.4 (65.0 - 78.0)	62.4 (57.7 – 64.8)	69.3 (67.0 - 71.7)

*Genotyped affected men are defined as affected men who were genotyped for at least 1 marker in the 1q24-25 region.

TABLE 1-3. TWO-POINT LOD SCORES FOR PROSTATE CANCER FAMILIES ANALYZED WITH MODELS S1, A, AND B.

			Recombination Fraction, θ							
Marker (cM from Preceding)	Number of Families	Model	0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
D1S1589 (---)	150	Model S1	-26.26	-20.60	-13.31	-8.71	-2.76	-0.61	-0.06	0
		Model A	-67.01	-40.46	-22.91	-14.28	-4.40	-1.04	-0.12	0
		Model B	-8.64	-7.18	-4.99	-3.44	-1.21	-0.32	-0.04	0
D1S2883 (2.84)	128	Model S1	-21.43	-16.41	-10.19	-6.44	-1.81	-0.27	0.02	0
		Model A	-52.86	-31.46	-19.29	-10.43	-2.89	-0.53	-0.02	0
		Model B	-6.69	-5.58	-3.90	-2.70	-0.96	-0.25	-0.02	0
D1S2818 (3.41)	129	Model S1	-18.42	-14.22	-9.06	-5.92	-1.90	-0.44	-0.05	0
		Model A	-47.73	-28.08	-15.44	-9.52	-2.95	-0.73	-0.10	0
		Model B	-4.93	-4.09	-2.81	-1.91	-0.62	-0.13	-0.01	0
D1S2127 (2.00)	137	Model S1	-18.81	-14.16	-8.74	-5.49	-1.42	-0.09	0.08	0
		Model A	-43.78	-26.17	-14.32	-8.63	-2.33	-0.35	0.03	0
		Model B	-4.80	-3.78	-2.38	-1.44	-0.21	0.13	0.09	0
D1S518 (1.89)	150	Model S1	-30.83	-24.11	-15.48	-10.07	-3.15	-0.69	-0.07	0
		Model A	-84.01	-50.47	-28.48	-17.71	-5.44	-1.28	-0.15	0
		Model B	-12.15	-9.95	-6.84	-4.71	-1.71	-0.48	-0.08	0
D1S1660 (10.25)	150	Model S1	-23.26	-17.19	-9.98	-5.82	-1.11	0.09	0.11	0
		Model A	-70.92	-40.53	-21.13	-12.25	-3.02	-0.42	0.02	0
		Model B	-4.89	-3.80	-2.22	-1.20	-0.02	0.19	0.09	0

TABLE 1-4. MULTIPOINT LOD SCORES FOR 150 PROSTATE CANCER FAMILIES.[A]

		Parametric			Non-parametric	
Marker	Distance (cM)	Lod	Hlod	α	NPL score	p-value
D1S1589	---	-39.87	-0.003	0.001	-0.65	0.74
D1S2883	2.84	-40.28	-0.004	0.009	-0.19	0.57
D1S2818	3.41	-39.54	0.017	0.026	0.15	0.43
D1S2127	2.00	-41.53	0.023	0.026	0.21	0.41
D1S518	1.89	-43.25	-0.002	0.0004	-0.19	0.57
D1S1660	10.25	-29.00	0.006	0.025	0.49	0.31

[a] Parametric lod scores , Hlod scores, and α's were calculated using model S1. Eleven families were not genotyped at markers D1S2883, D1S2818, and D1S2127.

TABLE 1-5. TWO-POINT LOD SCORES FOR STRATIFIED SUBSETS OF WHITE PROSTATE CANCER FAMILIES FOR MARKER D1S1589.

			Recombination Fraction							
Mean Age at Sampled Affected Men	Number of Families	Affected Men	0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	(n=66)	---	-21.45	-15.64	-9.77	-6.49	-2.37	-0.74	-0.14	0
≤60	(n=20)	---	-5.84	-4.13	-2.52	-1.67	-0.62	-0.21	-0.04	0
>65[a]	(n=78)	---	-13.23	-9.97	-5.99	-3.61	-0.75	0.05	0.08	0
≤65	(n=21)	5 or more	-6.55	-4.91	-3.10	-2.02	-0.65	-0.15	-0.02	0
≤65	(n=43)	in 2 gens.	-10.42	-7.50	-4.60	-3.00	-1.03	-0.29	-0.06	0

[a] All family groups were analyzed using Model S2, except this group which was analyzed with Model S3.

TABLE 1-6. TWO-POINT LOD SCORES FOR STRATIFIED SUBSETS OF WHITE PROSTATE CANCER FAMILIES FOR MARKER D1S518.

			Recombination Fraction							
Mean Age at Sampled Affected Men	Number of Families	Affected Men	0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	(n=66)	---	-34.50	-24.55	-15.23	-10.16	-3.88	-1.32	-0.29	0
≤60	(n=20)	---	-11.77	-8.70	-5.69	-3.99	-1.74	-0.67	-0.16	0
>65[a]	(n=78)	---	-12.49	-9.36	-5.44	-3.09	-0.36	0.26	0.14	0
≤65	(n=21)	5 or more	-16.60	-11.56	-7.17	-4.82	-1.89	-0.66	-0.15	0
≤65	(n=43)	in 2 gens.	-25.59	-18.06	-11.36	-7.73	-3.15	-1.16	-0.27	0

[a] All family groups were analyzed using Model S2, except this group which was analyzed with Model S3.

TABLE 1-7. TWO-POINT LOD SCORES FOR STRATIFIED SUBSETS OF WHITE PROSTATE CANCER FAMILIES FOR MARKER D1S1660.

			Recombination Fraction							
Mean Age at Sampled Affected Men	Number of Families	Affected Men	0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	(n=66)	---	-18.92	-13.07	-7.56	-4.69	-1.41	-0.32	-0.03	0
≤60	(n=20)	---	-7.11	-5.15	-3.21	-2.14	-0.80	-0.25	-0.05	0
>65[a]	(n=78)	---	-16.09	-11.82	-6.89	-4.09	-0.88	-0.01	0.06	0
≤65	(n=21)	5 or more	-7.04	-4.75	-2.71	-1.69	-0.54	-0.15	-0.03	0
≤65	(n=43)	in 2 gens.	-14.36	-9.73	-5.50	-3.35	-0.95	-0.20	-0.01	0

[a] All family groups were analyzed using Model S2, except this group which was analyzed with Model S3.

TABLE 1-8. MULTIPOINT LOD SCORES FOR STRATIFIED SUBSETS OF WHITE PROSTATE CANCER FAMILIES.

Family Group				Parametric			Non-parametric	
Mean Age at Sampled Affected Men	Number of Families	Affected Men	Marker, Distance (cM)	Lod θ=0	Hlod	α	NPL score	p-value
<65	(n=66)	---	D1S1589 (---)	-31.22	-0.001	0.0001	-1.49	0.94
			D1S2883 (2.84)	-34.87	-0.001	0.0002	-1.79	0.97
			D1S2818 (3.41)	-38.01	-0.0004	0.0001	-1.45	0.93
			D1S2127 (2.00)	-41.20	-0.0002	0.0000	-1.90	0.98
			D1S518 (1.89)	-42.74	-0.0002	0.0000	-1.67	0.96
			D1S1660 (10.25)	-29.54	-0.001	0.0001	-0.78	0.78
<60[a]	(n=20)	---	D1S1589 (---)	-9.13	-0.0003	0.0001	-1.21	0.89
			D1S2883 (2.84)	-11.79	-0.0003	0.0001	-1.60	0.95
			D1S2818 (3.41)	-12.92	-0.0002	0.0000	-1.43	0.93
			D1S2127 (2.00)	-12.11	-0.0002	0.0000	-1.35	0.92
			D1S518 (1.89)	-13.40	-0.0001	0.0000	-1.57	0.95
			D1S1660 (10.25)	-9.77	-0.0001	0.0000	-0.90	0.81
>65	(n=78)	---	D1S1589 (---)	-15.68	0.084	0.080	0.59	0.27
			D1S2883 (2.84)	-16.46	0.146	0.094	1.30	0.10
			D1S2818 (3.41)	-18.86	0.166	0.085	1.28	0.10
			D1S2127 (2.00)	-17.69	0.370	0.123	1.68	0.051
			D1S518 (1.89)	-17.56	0.023	0.044	1.22	0.11
			D1S1660 (10.25)	-17.85	-0.0001	0.022	0.78	0.22
<65	(n=21)	5 or more	D1S1589 (---)	-7.45	0.012	0.051	0.12	0.42
			D1S2883 (2.84)	-8.00	0.093	0.111	0.41	0.32
			D1S2818 (3.41)	-8.36	-0.001	0.002	-0.05	0.49
			D1S2127 (2.00)	-10.93	-0.0002	0.0001	-0.16	0.53
			D1S518 (1.89)	-13.23	-0.0002	0.0000	-0.58	0.70

TABLE 1-8 (CONTINUED). MULTIPOINT LOD SCORES FOR STRATIFIED SUBSETS OF WHITE PROSTATE CANCER FAMILIES.

Family Group				Parametric			Non-parametric	
Mean Age at Sampled Affected Men	Number of Families	Affected Men	Marker, Distance (cM)	Lod θ =0	Hlod	α	NPL score	p-value
			D1S1660 (10.25)	-7.98	-0.001	0.003	-0.14	0.52
<65	(n=43)	in 2 gens.	D1S1589 (---)	-29.36	-0.002	0.001	-0.27	0.60
			D1S2883 (2.84)	-34.50	-0.003	0.004	-0.47	0.67
			D1S2818 (3.41)	-35.51	0.031	0.032	0.09	0.45
			D1S2127 (2.00)	-38.27	0.020	0.024	0.12	0.44
			D1S518 (1.89)	-36.95	-0.001	0.001	-0.06	0.51
			D1S1660 (10.25)	-29.06	-0.002	0.001	-0.05	0.51

[a] Parametric lod scores, Hlod scores, and α's were calculated using Model S2, except this group which was analyzed with Model S3.

TABLE 1-9. PARAMETRIC TWO-POINT AND MULTIPOINT LOD SCORES FOR 46 WHITE PROSTATE CANCER FAMILIES WITH MINIMAL EVIDENCE OF LINKAGE TO OTHER LOCI. [A]

Model	Marker, Distance (cM)	Two-Point						Multipoint		
					Assuming Heterogeneity					
		Lod, $\theta = 0$	Maximum Lod	θ	Maximum Lod	θ	α	Lod	Hlod	α
S1	D1S1589 (---)	-5.02	0.10	0.32	0.10	0.32	0.06	-7.56	0.325	0.163
	D1S2883 (2.84)	-6.33	0.00	0.50	0.00	0.50	0.00	-7.24	0.429	0.181
	D1S2818 (3.41)	-3.35	0.17	0.28	0.17	0.28	0.00	-6.84	0.505	0.198
	D1S2127 (2.00)	-2.89	0.40	0.24	0.40	0.24	0.00	-8.88	0.113	0.099
	D1S518 (1.89)	-10.55	0.00	0.50	0.00	0.50	0.00	-12.00	-0.001	0.0003
	D1S1660 (10.25)	-8.17	0.01	0.42	0.01	0.42	0.00	-10.65	-0.001	0.001
A	D1S1589 (---)	-16.29	0.06	0.36	0.06	0.36	0.00	-22.39	0.017	0.038
	D1S2883 (2.84)	-21.89	0.00	0.50	0.00	0.50	0.00	-27.78	0.021	0.038
	D1S2818 (3.41)	-17.23	0.04	0.36	0.04	0.36	0.03	-30.11	0.027	0.040
	D1S2127 (2.00)	-11.96	0.24	0.28	0.24	0.28	0.00	-30.76	-0.003	0.006
	D1S518 (1.89)	-30.25	0.00	0.50	0.00	0.46	0.32	-33.76	-0.001	0.0001
	D1S1660 (10.25)	-22.97	0.00	0.50	0.00	0.50	0.00	-29.71	-0.0004	0.0001
B	D1S1589 (---)	-1.80	0.05	0.30	0.05	0.30	0.00	-2.74	0.071	0.139
	D1S2883 (2.84)	-2.50	0.00	0.50	0.00	0.50	0.00	-2.70	0.040	0.125
	D1S2818 (3.41)	-1.01	0.10	0.26	0.10	0.26	0.00	-3.36	-0.003	0.046
	D1S2127 (2.00)	-0.76	0.27	0.20	0.27	0.20	0.00	-4.42	-0.002	0.001
	D1S518 (1.89)	-6.05	0.00	0.50	0.00	0.50	0.00	-6.03	-0.001	0.0002
	D1S1660 (10.25)	-2.69	0.00	0.42	0.00	0.42	0.00	-4.20	-0.001	0.001

[a] Nonparametric multipoint analysis produced non-significant NPL scores throughout the region.

TABLE 1-10. TWO-POINT AND MULTIPOINT LOD SCORES FOR SUBGROUPS OF WHITE PROSTATE CANCER FAMILIES WITH MINIMAL EVIDENCE OF LINKAGE TO OTHER LOCI.

Family Group	Marker, Distance	Two-Point						Multipoint				
				Assuming Heterogeneity				Parametric			Non-parametric	
		Lod, $\theta = 0$	Maximum Lod	θ	Maximum Lod	θ	α	Lod	Hlod	α	NPL score	p-value
24 families, mean age at diagnosis < 65 years	D1S1589	-5.62	0.02	0.34	0.02	0.32	0.29	-8.81	-0.002	0.003	-0.65	0.74
	D1S2883	-6.62	0.00	0.50	0.00	0.00	0.00	-9.06	-0.002	0.011	-0.79	0.78
	D1S2818	-3.56	0.31	0.24	0.31	0.24	0.00	-9.74	0.003	0.027	-0.25	0.58
	D1S2127	-4.59	0.03	0.36	0.03	0.36	0.00	-12.63	-0.001	0.001	-0.78	0.78
	D1S518	-13.91	0.00	0.50	0.00	0.00	0.00	-14.35	-0.0004	0.0002	-0.85	0.80
	D1S1660	-7.06	0.00	0.44	0.00	0.44	0.00	-10.82	-0.001	0.0003	-0.28	0.59
9 families, mean age at diagnosis < 60 years	D1S1589	-2.57	0.00	0.50	0.00	0.50	0.00	-3.46	-0.001	0.004	-0.66	0.74
	D1S2883	-4.45	0.00	0.50	0.00	0.50	0.00	-4.37	-0.001	0.002	-1.00	0.84
	D1S2818	-3.20	0.00	0.50	0.00	0.50	0.00	-4.43	-0.001	0.001	-0.44	0.66
	D1S2127	0.31	0.31	0.00	0.31	0.00	0.07	-4.29	-0.001	0.001	-0.43	0.65
	D1S518	-5.94	0.00	0.50	0.00	0.50	0.00	-5.62	-0.0001	0.0001	-0.70	0.75
	D1S1660	-3.32	0.00	0.50	0.00	0.50	0.00	-3.78	-0.0002	0.0001	-0.09	0.52
21 families, mean age at diagnosis > 65 years [a]	D1S1589	-1.99	0.06	0.34	0.06	0.34	0.00	-2.98	0.041	0.117	0.62	0.26
	D1S2883	-2.69	0.03	0.36	0.03	0.36	0.00	-3.65	0.026	0.092	0.70	0.24
	D1S2818	-2.96	0.00	0.50	0.00	0.50	0.00	-5.16	-0.001	0.001	0.39	0.34
	D1S2127	-1.65	0.35	0.22	0.35	0.22	0.00	-5.09	-0.001	0.001	0.45	0.32
	D1S518	-2.85	0.00	0.50	0.00	0.50	0.00	-4.95	-0.0003	0.0002	0.10	0.44
	D1S1660	-4.54	0.00	0.42	0.00	0.42	0.00	-5.26	-0.001	0.002	-0.06	0.51
8 families, mean age at diagnosis < 65 years, 5	D1S1589	-1.94	0.10	0.26	0.10	0.26	0.00	-3.78	-0.0002	0.0001	-0.05	0.66
	D1S2883	-1.27	0.03	0.32	0.03	0.32	0.00	-3.72	-0.0001	0.0001	-0.66	0.71
	D1S2818	-0.09	0.40	0.12	0.40	0.12	0.00	-5.25	-0.0000	0.0000	-0.77	0.77
	D1S2127	-2.30	0.07	0.30	0.07	0.30	0.00	-5.63	-0.0000	0.0000	-0.90	0.82

TABLE 1-10 (CONTINUED). TWO-POINT AND MULTIPOINT LOD SCORES FOR SUBGROUPS OF WHITE PROSTATE CANCER FAMILIES WITH MINIMAL EVIDENCE OF LINKAGE TO OTHER LOCI.

Family Group	Marker, Distance	Two-Point						Multipoint				
				Assuming Heterogeneity				Parametric			Non-parametric	
		Lod, θ = 0	Maximum Lod	θ	Maximum Lod	θ	α	Lod	Hlod	α	NPL score	p-value
or more affected men per family	D1S518	-6.22	0.00	0.50	0.00	0.50	0.00	-6.91	-0.0000	0.0000	-1.01	0.85
	D1S1660	-3.63	0.00	0.50	0.00	0.50	0.00	-5.66	-0.0000	0.0000	-0.91	0.82
19 families, mean age at diagnosis < 65 years, prostate cancer in more than one generation	D1S1589	-4.37	0.00	0.50	0.00	0.50	0.00	-5.38	0.120	0.130	0.01	0.48
	D1S2883	-3.94	0.04	0.32	0.04	0.32	0.00	-6.09	0.190	0.147	-0.08	0.51
	D1S2818	-2.97	0.01	0.36	0.01	0.36	0.00	-7.77	0.074	0.090	-0.03	0.49
	D1S2127	-3.48	0.13	0.24	0.13	0.24	0.00	-8.26	0.039	0.069	-0.11	0.53
	D1S518	-10.61	0.00	0.50	0.00	0.50	0.00	-10.82	-0.001	0.001	-0.43	0.65
	D1S1660	-5.57	0.04	0.32	0.04	0.32	0.00	-7.60	-0.001	0.001	0.14	0.43

[a] Parametric lod scores, Hlod scores, and α's were calculated using Model S2, except this group which was analyzed using Model S3

CHAPTER 2 CLINICAL CHARACTERISTICS OF PROSTATE CANCER IN AN ANALYSIS OF LINKAGE TO 4 PUTATIVE SUSCEPTIBILITY LOCI

Introduction

Prostate cancer is a significant cause of morbidity and mortality in the United States. In 2000, there will be an estimated 180,400 new prostate cancer cases in the U.S. and 31,900 deaths due to the disease (Greenlee et al., 2000). Age, race, and family history are the strongest risk factors for prostate cancer. African-American men have the highest incidence of prostate cancer in the world, and Asian men have the lowest incidence (American Cancer Society, 1999). A number of potentially modifiable environmental risk factors for prostate cancer have been studied, including industrial exposures, sexual activity, sexually transmitted infectious agents, alcohol, and diet (Dijkman et al., 1996; Ross et al., 1996). Diet may be the most influential modifiable risk factor; dietary fat, cruciferous vegetables, vitamin E supplementation, selenium, and lycopene have been implicated in some studies (Kolonel et al., 1988; West et al., 1991; Corder et al., 1993; Giovannucci et al., 1993; Clinton et al., 1996; Clark et al., 1998; Heinonen et al., 1998; Sies et al., 1998; Zhao et al., 1998; Cohen, 2000). However, no particular environmental factor has been identified as a major cause of the disease (Ross et al., 1996).

Family history of prostate cancer increases risk 2- to 4- fold, indicating that genetics plays a role in prostate cancer (Fincham et al., 1990; Whittemore et al., 1995; Grönberg et al., 1996). Numerous case-control studies have attempted to evaluated risk

associated with polymorphisms of several genes including CYP3A4 (Rebbeck et al., 1998), CYP17 (Wadelius, 1999), glutathione s-transferase-T1 (Rebbeck et al., 1999), vitamin D receptor (Kibel et al., 1998; Ma et al., 1998), CAG and GGN repeat length in the androgen receptor, (Giovannucci et al., 1997; Ingles et al., 1997; Stanford et al., 1997), and the PSA gene (Xue et al., 2000). Due to their more common frequencies in the general population, alleles of these candidate genes may confer higher population attributable risk than the rarer, highly penetrant major genes localized by linkage analyses.

The existence of rare, highly penetrant susceptibility genes for prostate cancer has been supported by studies of high-risk prostate cancer families. Complex segregation analyses have provided evidence for autosomal dominant inheritance of prostate cancer genes with estimated frequencies of 0.36 to 1.67 percent and lifetime penetrances of 63 to 89 percent (Carter et al., 1992; Grönberg et al., 1997a; Schaid et al., 1998). Linkage analyses of genetic markers distributed throughout the genome (genome scans) have indicated several regions that may be involved in inherited prostate cancer (Smith et al., 1996; Berthon et al., 1998; Berry et al., 2000b; Gibbs et al., 2000; Suarez et al., 2000; Witte et al., 2000). Evidence for the locus *HPC1* in the 1q24-25 chromosomal region was first observed at marker D1S218 (lod = 3.65, $\theta = 0.18$) in a collection of North American and Swedish families (Smith et al., 1996). Confirmation linkage studies at 1q24-25 have had mixed results (Cooney et al., 1997; Hsieh et al., 1997; McIndoe et al., 1997; Berthon et al., 1998; Eeles et al., 1998; Berry et al., 2000a; Goode et al., 2000; Neuhausen et al., 2000). A combined dataset of 772 families from 9 research groups

estimated that 6 percent of families were linked, revealing a peak multipoint Hlod of 1.40 ($p = 0.01$) at D1S212 (Xu, 2000). A second locus called *PCaP* at 1q42.2-43 was identified in an genome-wide analysis of 47 French and German families (Berthon et al., 1998). A two-point lod score of 2.7 observed with marker D1S2785 rose to 3.31 when restricted to families with mean age at onset < 60 years (Berthon et al., 1998). Studies of *PCaP* in other collections of families have not revealed statistically significant evidence for linkage, but 4 to 9 percent of families have been estimated to be linked (Gibbs et al., 1999a; Whittemore et al., 1999; Berry et al., 2000a). Linkage to a third locus called *HPCX* at Xq27-28 was seen in an analysis of 360 prostate cancer families combined from 4 research groups; a maximum two-point lod score of 4.60 was observed at marker DXS1113 ($\theta = 0.26$) (Xu et al., 1998b). Studies seeking to confirm linkage to *HPCX* have suggested that a small percentage of prostate cancer families may be linked (Lange et al., 1999; Peters et al., (in press)). A fourth locus called *CAPB* at 1p36 was identified in a subset of prostate cancer families that also had a family history of primary brain cancer at marker D1S507 (lod = 3.22, $\theta = 0.06$) (Gibbs et al., 1999b). Other studies of *CAPB* in prostate cancer families with brain cancer produce disparate results (Berry et al., 2000a; Badzioch et al., personal communication). A genome-wide scan of 162 North American families found evidence for linkage to a fifth putative locus called *HPC20* at 20q13 with lod = 2.69 (θ=0.20) at D20S196 and NPL = 3.94 (p=0.00007) at D20S887 (Berry et al., 2000b). It seems likely that hereditary prostate cancer is a genetically heterogeneous disease, with several genes conferring susceptibility.

Some studies indicate that men with inherited cases of prostate cancer may differ clinically from sporadic cases (Bastacky et al., 1995; Keetch et al., 1996; Kupelian et al., 1997a; Kupelian et al., 1997b; Norrish et al., 1999). A study of prostate cancer families originally analyzed at the *HPC1* locus assessed clinical differences between "potentially-linked" and "potentially-unlinked" families based on haplotype sharing among affected men, and they found that affected men in families "potentially-linked" to *HPC1* were younger at diagnosis and more likely to have high-grade tumors and advanced stage disease (Grönberg et al., 1997b).

Grouping families with similar clinical characteristics, e.g. age at diagnosis, can increase the power of linkage studies (Xu et al., 1998a) and has proven useful in elucidating linkage to susceptibility genes for several diseases including breast cancer and Alzheimer disease (Hall et al., 1990; Futreal et al., 1994; Miki et al., 1994; Pericak-Vance et al., 1997). Age at diagnosis and the presence of other cancers have assisted in prostate cancer linkage studies as well, based on the idea that similar clinical phenotypes may have similar genetic causes (Berthon et al., 1998; Gibbs et al., 1999b). Consideration of characteristics of the cancer such as tumor grade and cancer stage may further define linked subgroups of families. One prostate cancer genome scan considered disease as a quantitative trait using Gleason score (range 2-10), a measure of cellular differentiation, in Haseman-Elston linkage analysis (Witte et al., 2000). They found several regions of interest, including some linkage near the *CAPB* region ($p < 0.01$) indicating that *CAPB* may be involved in high-grade disease. Consideration of clinical characteristics in other datasets may help elucidate the role of *HPC1*, *PCaP*, *HPCX*, and *CAPB* in inherited prostate cancer.

Methods

Study Subjects

Families with 3 or more cases of prostate cancer were recruited starting in 1995 to participate in the Prostate Cancer Genetic Research Study (PROGRESS). A toll-free telephone number (1-800-777-3035) was distributed nationally that encouraged families with several cases of prostate cancer to inquire about participation in a genetic research study. In addition, communications with urologists, prostate cancer support groups, and health related publications facilitated recruitment of families. To be eligible, families of callers must have had either of the following: 1) three or more first-degree relatives with prostate cancer, 2) prostate cancer in three successive generations, or 3) prostate cancer in two living first-degree relatives diagnosed before age 65 years. African-American families were selected if they had two or more living affected men. All study materials and procedures for this ongoing study were approved by the Fred Hutchinson Cancer Research Center's institutional review board. Family members completed study questionnaires and submitted blood samples, and affected men consented for the request of medical records related to their prostate cancer diagnosis and treatment. Additional information on family recruitment and sample collection is available elsewhere (McIndoe et al., 1997; Gibbs et al., 1999a).

Clinical Data

Prostate cancer diagnoses were confirmed by medical records and death certificates. Since the reporting of cancer diagnosis by 2nd or 3rd degree relatives has

been shown to be unreliable, the pedigrees used in this analysis were reduced so that affected family members who were not sampled (deceased or no contact) and who were more than 1 generation away from a sampled individual were excluded (Steinberg et al., 1990; Bondy et al., 1994). Because reporting of prostate cancer by first-degree relatives has been shown to be fairly sensitive (70 percent, (Kerber et al., 1997)), ungenotyped affected men were included in this analysis if they were a first-degree relative of a participating individual. Family structure inaccuracies made apparent by Mendelian inconsistencies at markers in the 4 regions analyzed here, X and Y chromosome analysis, and at 380 markers throughout the genome (94 families) were corrected when possible using haplotype analysis, investigations of possible sample switches, and the use of the computer program RELPAIR (Duren et al., 1997). Age at diagnosis of all participating affected men was determined from medical record or written self report. Additional clinical data were abstracted from the medical records of affected men including results of digital rectal exam, pre-diagnosis prostate-specific antigen (PSA) level, date of diagnosis, Gleason score on biopsy, Gleason score on prostatectomy sample (if surgery performed), tumor grade (if specific Gleason score was unavailable), clinical stage, pathologic stage (if surgery performed), extent of tumor spread at surgery (if surgery performed), and primary treatment. The medical record form used is included in Appendix B. Unaffected men aged 45 years or older were coded as having unknown affected status if they indicated on the questionnaire that they had not had a prostate-specific antigen (PSA) test within the last 5 years, if they didn't know if they had had a PSA test, or if they had an elevated or abnormal PSA and did not have physician diagnosed benign prostatic hyperplasia (BPH).

Tumor Grade. Over 95% of primary prostate cancers are adenocarcinomas of the prostatic acini (cells which line the epithelial ducts of the prostate gland. When the cancer occurs, the acini undergo a characteristic histologic change and are altered in size and shape to a variable degree. Well-differentiated tumors maintain the normal acinar structure, while poorly differentiated tumors show great disruption of the normal acinar pattern and little or no differentiation of epithelial cells into gland (Paulson, 1987). In general, the abnormality of histologic growth and the degree of tumor differentiation directly correlate with likelihood of metastases and with death. Poorly differentiated tumors are more likely to have already metastasized and are associated with a poorer prognosis (Paulson, 1987; Cheng et al., 1999). The AJCC confers a histopathologic grade ranging from I to IV based on the amount of differentiation (American Joint Committee on Cancer, 1997).

The Gleason grading system is widely used to classify the histopathologic grade of the tumor (Paulson, 1987). Because most prostate adenocarcinomas express more than one histologic glandular pattern, the Gleason system records a score which ranges from 1 to 5 for the two predominant patterns in a given tumor (for example 4 and 3). These two patterns are added together to give a Gleason sum score ranging from 2 to 10 (for example, 4 + 3 = 7) (Gleason et al., 1974; Gleason, 1977)). Table D-1 indicates classifications of prostate cancer grading systems. Tumors with low Gleason scores tend to be small in volume and have low metastatic potential. Tumors with high Gleason scores tend to be large in volume and have significant metastatic potential. The preoperative Gleason score correlates closely with prostatic capsular penetration, seminal vesicle invasion, pelvic lymph node metastasis, and distant metastasis (Gleason, 1977).

Tumor grade in this analysis was obtained from pathologic reports of prostatectomy specimen, if available, otherwise from pathologic reports of the biopsy specimen. Surgical specimens allow for a larger amount of tissue to be reviewed by a pathologist and result in fewer sampling errors. Biopsy specimens have been shown to be accurate (same as the protatectomy specimen) in terms of grade 71% of the time, with 23% undergraded and 6% overgraded at biopsy (Johnstone et al., 1995). Grade classification were: 1) low-grade (well-differentiated, Grade I, Gleason score 2 to 4), 2) moderate-grade (moderately-differentiated, Grade II, Gleason score 5 to 7), and 3) high-grade (poorly-differentiated, Grade III, Gleason 8 to 10).

Tumor Stage. Treatment and survival of patients with prostate cancer is related to the extent of tumor, as summarized by the cancer's stage. When the cancer is confined to the prostate gland, the disease is frequently curable, but if prostate cancer has spread to distant organs, current therapy will not cure it. Both clinical and pathologic staging allow physicians to determine treatment, evaluate results of management, and to compare world-wide statistics (American Joint Committee on Cancer, 1997). Clinical staging is based on evidence acquired before primary treatment, and is used as a guide to the selection of primary therapy (American Joint Committee on Cancer, 1997). Pathologic staging includes the evidence acquired before treatment, supplemented or modified by the additional evidence acquired during and from surgery, particularly the pathologic examination. Pathological evaluation following prostatectomy stratifies tumor extent into organ-confined, specimen-confined, and margin-positive disease. The incidence of disease recurrence increases when the tumor is not specimen-confined (extracapsular) and/or the margins are positive (Adolfsson et al., 1994; Johansson et al., 1997).

Two systems are in common use for the staging of prostate cancer. One system is the Jewett system (stages A through D) which was first described in 1975 (Jewett, 1975) and has since been modified. Table D-2 describes the Jewett system in detail. Generally, Stage A describes prostate cancers that are incidental findings, Stage B describes cancer confined to the prostate gland, Stage C describes cancer extending through the prostatic capsule or involving the seminal vesicles, and Stage D describes prostate cancer that has metastasized. The second staging system is the TNM system which was adopted by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer in 1992. Table D-3 describes the TNM system in detail. This system is based on three significant events in the life history of a cancer: local tumor growth (T), spread to regional lymph nodes (N), and distant metastases (M) (American Joint Committee on Cancer, 1997). The AJCC also groups TNM stages into broader stage categories from I to IV as shown in Table D-4.

In this analysis, tumor stage consisted of pathologic stage, if available, or clinical stage, if pathologic stage was unavailable. The TNM staging system was used to record clinical stage, and this system is based on the three significant events in the natural history of a cancer: local tumor growth (T), spread to regional lymph nodes (N), and distant metastases (M) (American Joint Committee on Cancer, 1997). The Jewet staging system was used to record both clinical and pathologic stage. In most analyses, tumor stage was classified as follows: 1) localized disease (Stage A or B), 2) regionally-spread disease (Stage C), and 3) distantly-metastasized disease (Stage D).

Aggressive Disease. Affected men with medical record data were considered to have "aggressive" disease if they had a high-grade tumor or had cancer that had spread beyond the prostate (Stage C or D).

Genotyping

Individuals in 149 families were genotyped using microsatellite markers in the *HPC1* (1q24-25), *PCaP* (1q42.2-43), *HPCX* (Xq27-28), and *CAPB* (1p36) regions. Chromosomal locations of all markers analyzed are presented in Appendix B. In the *HPC1* region, families were genotyped at markers D1S1589, D1S518, and D1S1660, and a subset of 139 families with additional available DNA were also genotyped at *HPC1* markers D1S2883, D1S2818, and D1S2127. These 6 *HPC1* markers are arranged on 1q24-25 using the sex-averaged map from the Marshfield Medical Research Foundation as follows: D1S1589--2.84 cM--D1S2883--3.41 cM--D1S2818--2.00 cM--D1S2127--1.89 cM--D1S518--10.25 cM--D1S1660. These 6 markers surround the region identified by Smith et al. (1996) as likely to contain *HPC1* and lie within the region defined by the *HPC1* combined analysis (Xu, 2000). The following markers were analyzed in the 1q42.2-43 *PCaP* region, including those with peak lod scores in the original linkage paper (Berthon et al., 1998): D1S235—11.63 cM—D1S2785—1.24 cM—D1S547—8.26 cM—D1S1609. In the Xq27-28 region thought to contain *HPCX*, the following markers were analyzed, including those with peak lod scores in the original linkage paper (Xu et al., 1998b): DXS984—5.2 cM--DXS8106—1.2 cM--DXS6806—3.1 cM—DXS1200—0.6 cM--DXS297—2.3 cM—DXS1193—1.2 cM—DXS8069—0.7cM—DXS8103. In the *CAPB* region, families were genotyped at markers D1S1597 and D1S407 which are

3.82 cM apart on 1p36. Additional information about genotyping of DNA samples is summarized elsewhere (McIndoe et al., 1997; Gibbs et al., 1999a). Because of the relatively large number of ungenotyped founders, allele frequencies were determined using all individuals in the dataset. Though these individuals were not independent, it has been shown that, asymptotically, this gives an unbiased estimate in large sets of pedigrees with founders often untyped. Further, any bias that could occur would be conservative, because the allele which appears to be cosegregating with the disease would be overestimated more than underestimated with this approach (Ott, 1992; Terwilliger et al., 1994).

Statistical Analysis

Method. The lod score method of linkage analysis was used to test the null hypothesis that there is no linkage between the genetic markers and the putative prostate cancer susceptibility gene. If there is no linkage, 2 loci will be transmitted together from parent to child on average half of the time and, therefore, the recombination fraction (θ) between the loci will be 0.5. When linkage exists, two loci will be co-transmitted more than half of the time, and θ will be less than 0.5. A lod score represents the log base 10 of the ratio of the likelihood given a particular θ between a marker and the putative disease gene to the likelihood at $\theta = 0.5$. Lod scores greater than 3.0 have traditionally been considered significant evidence for linkage for Mendelian diseases, while lod scores less than -2.0 are considered evidence against linkage (Morton, 1955; Ott, 1999). To account for multiple markers being tested in genome-wide scans of complex diseases, it has recently been suggested that the lod score threshold for significance be increased to

3.3, corresponding to a p-value of 4.9×10^{-5} (Lander et al., 1995). The value of θ at which the lod score peaks is the maximum likelihood estimate of θ.

Parametric lod score analyses rely on a model for the transmission of the disease gene. Several models for the transmission of prostate cancer were used in this analysis, all of which assumed a disease gene frequency of 0.003 derived from the segregation analysis of Carter et al. (1992). Analyses of *HPC1*, *PCaP*, and *CAPB* markers assumed autosomal dominant transmission, and analyses of *HPCX* markers assumed X-linked dominant transmission. Model B+, which is based on Model B of Grönberg et al. (1997c), is described in Table 2-1. It is an age-dependent penetrance model, based on the cumulative distribution function for unaffected men and probability density function for affected men, similar to Easton et al. (1993). This model features decreasing penetrance ratios with increasing age, representing a higher probability of younger cases to be genetic than older cases. Here, the only difference from Model B of Gronberg et al. (1997) is the assignment of zero risk for prostate cancer to men under 30 years of age. To eliminate the possibility that a failure to replicate prior linkage results would be due to a difference in model specifications, models from other studies that found significant evidence for linkage were also used. *HPC1* analyses were also performed using Model A from the original *HPC1* linkage analysis (Smith et al., 1996) and Model B from follow-up *HPC1* analyses (Grönberg et al., 1997c). *PCaP* analyses were also run with Models 1 and 2 from the original *PCaP* linkage study (Berthon et al., 1998). *HPCX* analyses were also performed using the X-linked variation of Model A used for the original finding of linkage to *HPCX* (Xu et al., 1998b).

Two-point (one marker and the disease gene) parametric analyses testing the transmission of disease with one marker at a time were conducted using the program LINKAGE (Fastlink, analyze) v 5.1 (Ott, 1976). Two-point analysis was also performed assuming locus heterogeneity. Under this assumption, a proportion (α) of families are assumed to be linked to the locus being investigated, and a proportion ($1-\alpha$) are assumed not to be linked. Lod scores are calculated at incremental values of α , and a lod score assuming heterogeneity (Hlod) represents the maximum lod score obtained over varying values of both α and θ . The program HOMOG was used for heterogeneity analysis and estimation of α (Ott, 1991). Estimates of α without the inclusion of confidence contours should not be overinterpreted.

Multipoint parametric analysis assesses the coinheritance of multiple markers (a haplotype) with the disease, rather than just one marker at a time. This method can be more powerful than 2-point analysis when the genetic model is specified correctly and when the marker map is correct (Xu et al., 1998a). Parametric multipoint analysis was performed assuming homogeneity (producing multipoint lod scores) and assuming heterogeneity, yielding parametric multipoint Hlod scores and estimates of α (which may be underestimates due to the inability of multipoint analysis to vary θ). Multipoint non-parametric linkage (NPL) analysis which does not require a genetic model of prostate cancer be specified was also performed. The resulting NPL_{ALL} score and corresponding p-value represents a measure of haplotype-sharing among all affected individuals in each family (Whittemore et al., 1994). Multipoint analysis of *HPC1*, *PCaP*, and *CAPB* used the program GENEHUNTER v. 2.0 (Kruglyak et al., 1996; Markianos et al., 1999), and analysis at *HPCX* used GENEHUNTER-PLUS v. 1.2 (Kong et al., 1997).

Stratification of families. Because clinically similar phenotypes may result from common genetic pathways, we attempted to create homogeneous subsets of families by grouping them based on affected men having similar disease characteristics. We aimed to increase the power of the analysis, observe differences between groups and identify characteristics which may describe families with the most evidence for linkage. The power of linkage analysis is increased when the families analyzed are genetically homogeneous (Ott, 1999). To improve this homogeneity, we restricted all stratified analyses to white families. Families were then stratified by median age at diagnosis, distributions of tumor grade and cancer stage, and a summary variable of "aggressive" disease. These stratified analyses were also conducted with further stratification by median age at diagnosis, number of affected men, and evidence of linkage to other loci.

Median age at diagnosis per family (< 60 years, 60-64 years, 65-69 years, and 70+ years) was calculated using the ages of diagnosis of all affected men on whom medical records were available or who provided a written self-report of age at diagnosis. Median age may better represent the age clustering of affected men in a family than mean age, being less sensitive to outliers.

The distribution of tumor grade and stage in each family was described. White families were classified according to distribution of tumor grade as follows: 1) only low grade tumors, 2) low and moderate grade tumors, 3) only moderate grade tumors, 4) low, moderate, and high grade tumors, 5) moderate and high grade tumors or 6) only high grade tumors. For most analyses, grade groups 1 and 2 were combined, and grade groups 4, 5, and 6 were combined. Families were classified according to distribution of cancer

stage as follows: 1) only localized disease, 2) localized and regionally spread disease, 3) only regionally spread disease, 4) localized, regionally spread, and distantly metastasized disease, 5) regionally spread and distantly metastasized disease 6) only distantly metastasized disease. For most analyses, stage groups 2 and 3 were combined, and stage groups 4, 5, and 6 were combined.

The percentage of prostate cancers that were considered to be "aggressive" was also then used to group families as follows: 1) no "aggressive" disease; 2) at least one case with "aggressive "disease, but less than 50 percent of affected men; 3) 50 percent of affected men or more had "aggressive" disease; and 4) all men had "aggressive" disease (a subset of the preceding group).

HPC1 analyses were also stratified by the last year of diagnosis per family, in order to attempt replication of a recent finding that more evidence for *HPC1* linkage was observed among families with men all diagnosed before 1990 than families with men diagnosed before 1996 (Xu et al., 2000).

For the analysis at *HPCX*, white families were also stratified by putative inheritance pattern. Linkage to an X-linked susceptibility locus would not be consistent with male-to-male disease transmission, because an X-linked disease allele may only be passed from mother to child. Families were classified in the same manner as the original observation of *HPCX* linkage (Xu et al., 1998b) as follows: 1) "male-to-male" transmission indicates an a family includes an affected father and son or prostate cancer on paternal side only; 2) "not male-to-male" indicates a family without an affected father

and son or with prostate cancer on maternal side; and 3) "siblings only" indicates an unknown transmission pattern because prostate cancer is only present in one sibship.

To minimize heterogeneity based on other putative loci, all stratified analyses were repeated removing families with possible evidence for linkage to other loci. Evidence for potential linkage to other loci was defined as having a lod score ≥ 0.1 at any θ at markers in the *HPC1* region (D1S518), *PCaP* region (D1S2785), *HPCX* region (DXS984), or *CAPB* region (D1S407). This cut-off of lod < 0.1 was chosen because approximately half of the dataset was removed for each analysis, leaving reasonable sample sizes while eliminating families that may be linked to other loci.

Results

One hundred and forty-nine high-risk prostate cancer families (2,410 individuals), including 662 affected men, were ascertained nationally*. Family relationships were adjusted for 14 families based on investigation of Mendelian inconsistencies. There was an average of 4.2 affected men per family (range, 3 - 14), and the median age at diagnosis of sampled affected men per family was 67.0 years (range, 51.5 – 78.0). Six families were non-white. One thousand two-hundred and thirty-three people, including 514 affected men were genotyped at *HPC1*, *PCaP*, *HPCX*, and *CAPB* markers. Fifty-eight unaffected men aged 45 years or older who reported no normal PSA test within the past 5 years were coded as having an unknown affected status (see Methods).

* One family analyzed in Chapter 1 was removed from this analysis because a newly-discovered Mendelian inconsistency raised questions about the family structure.

Clinical Data

Medical records confirming adenocarcinoma of the prostate diagnosis were available for 505 affected men, with an average of 3.4 affected men per family having medical record data (range, 1 – 9). Table 2-2 describes the clinical data of affected men with medical records. Affected men were diagnosed between 1974 and 1999, and 85 percent were diagnosed after 1987. Three hundred sixty-four affected men (72 percent) had an elevated PSA at the time of diagnosis, and 282 (56 percent) had an abnormal DRE at the time of diagnosis, however it is difficult to establish which screening method initially suggested prostate cancer. Fifty-six men (11 percent) had microscopic, unpalpable, unvisualizable cancer that was only detected by PSA screening (stage T1cNxMx) (American Joint Committee on Cancer, 1997). PSA values and year of diagnosis are shown in Table E-1. Pathology reports from biopsy were available for 331 men and from prostatectomy for 232 men (90 percent of those who had prostatectomy). One hundred and forty-six men had both pathology reports from biopsy and surgery.

Tumor grade data were available for 471 affected men and represent information from a surgical specimen if available. The majority of men (67 percent) had moderately differentiated tumors (Table 2-2). Table E-2 and Table E-3 indicate the PSA values of men with different grades of disease; men with poorly differentiated disease were likely to have elevated PSA values > 20 ng/ml at diagnosis. Pathologic analysis of the prostate itself can result in a different classification of histologic grade of the surgical specimen than the biopsy specimen in as much as 25-40 percent of cases (Garnett et al., 1984; D'Amico et al., 1999; Iczkowski et al., 1999). Of 174 men with known Gleason score at

biopsy and known grade from prostatectomy specimens, 33 men (19 percent) were "upgraded" when the entire prostate was examined (20 from low to moderate grade, 11 from moderate to high grade, and 2 from low to high grade), and 8 men (5 percent) were "downgraded" (3 from moderate to low grade and 5 from high to moderate grade) (Table E-11).

Clinical stage was available for 471 men (93 percent) (Table 2-2). The clinical stage for 427 men (85 percent) indicated that the cancer was localized (Stage A or B). Two-hundred and fifty-seven men had primary treatment of prostatectomy, and pathologic stage was available for 237 of these men. Twenty-five men had unknown clinical stage, but because they were treated with prostatectomy, they were assumed to have had localized disease (clinical Stage A or B). Table E-4, Table E-5, and Table E-6 indicate the PSA values of men with different stages; men with regional or distant disease were likely to have an elevated PSA at diagnosis. In the general population, up to 50-59 percent of cases are upstaged at prostatectomy meaning that because of their surgery, the cancer was found to have spread to a larger extent than was suspected at initial clinical examination (Bostwick, 1997; Selley et al., 1997). Of 236 men in the current analysis with known clinical and pathologic stage, 74 men (31 percent) were "upstaged" from having localized disease at prostatectomy including 63 (27 percent) men found to have regional spread and 11 men (5 percent) found to have lymph node involvement or other metastases (Table E-12). Using pathologic stage, if available (237 men), to indicate the summary cancer stage, 353 men (70 percent) had localized disease, while 89 men (18 percent) had regional spread, 29 men (6 percent) had metastasis to bone or lymph node (Stage D), and 34 men (7 percent) had unknown stage (Table 2-2).

Among 452 men with known grade and stage, grade and stage were correlated ($\chi^2 = 27.36$, $p < 0.001$), consistent with population-based data (Table E-7). Only 6 percent of men with localized disease had poorly differentiated tumors, while 21 percent of men with regional or distantly metastasized disease did. Considering grade and stage simultaneously, 351 men (69 percent) had "aggressive disease" (high-grade, regionally-spread, or distantly metastasized disease).

Clinical information by family is summarized in Table 2-3. Ninety-one percent of families analyzed included men who were diagnosed in 1992 or after. Only 3 families included men who were all diagnosed before 1990, at which point PSA screening became commonplace. Therefore, the majority of families analyzed were expected to include cases that were detected by PSA screening. The majority of families contained only moderate grade disease (40%) and 32 percent consisted of both low and moderate grade disease. Twelve percent of families (11% of white families) contained low, moderate, and high-grade disease. Six families (5 white families) included more than one man with high-grade disease. Regarding stage, the majority of families (42 percent of all families, 44 percent of white families) included only localized disease (Stage A or B) (Table 2-3). Thirty-seven percent of families (26 percent of white families) contained localized and regional disease (Stage A or B and Stage C). Three families included more than one man with distantly-metastasized disease. Grade and stage data were combined to represent aggressive disease (high-grade or regionally-spread or distantly metastasized disease). The percentage of cases in a family that met the aggressive disease criteria was then calculated, and most families (42% of all families, 41% of white families) contained at

least one case, but less than half. Fifty-three families did not include any men with aggressive disease (Table 2-3). One hundred twenty-four families had at least one man who had prostatectomy.

Analysis of *HPC1*

All Families. In the dataset as a whole, there was no significant evidence for linkage to *HPC1* markers in the 1q24-25 region (Table 2-4). Using Model B+, 2-point lod scores became positive at higher θs with a peak lod of 0.43 (θ= 0.24) at marker D1S1660. Multipoint lod, Hlods and NPL scores were also negative. Analysis of the 149 families considering models used in the original finding of *HPC1* linkage produced negative results as well. Seventy-one families with lod scores >= 0.1 at *PCaP* (D1S2785), *HPCX* (DXS894), or *CAPB* (D1S407) were excluded, and a peak 2-point lod score of 0.39 (θ =0.16) was seen at D1S2818. Multipoint analysis of the remaining 78 families yielded positive but non-significant NPL scores at all markers, with a peak NPL of 0.98 (p=0.16) at D1S2883 (Table 2-4).

Median Age. When white families were stratified by median age at diagnosis of sampled affected men, the oldest onset families had the most evidence for linkage to *HPC1* markers (Table 2-5). While groups of families with median age at diagnosis < 60 years, 60 – 64 years, and 65 - 69 years had few positive 2-point lod scores and no positive multipoint lod scores, the 42 families with median age at diagnosis ≥ 70 years had positive 2-point and multipoint lod scores at all *HPC1* markers. These older onset families had a peak 2-point lod score of 1.52 (θ = 0) at marker D1S518, and positive

multipoint lod and NPL scores at all *HPC1* markers. NPL scores in this group of older families were > 1.24 for markers D1S2883, D1S2818, D1S2127, and D1S1660. When families with evidence for possible linkage at other loci were excluded, positive NPL scores were seen in the two older-onset family groups (median ages 65-69 and 70+ years) (Table 2-5). The group of 38 families with median age $\geq$ 70 years and minimal evidence for other linkage produced lower lod scores for linkage after removal of families possibly linked to other loci. This diminishing evidence for linkage in the oldest onset group may be due to decreased sample size or may indicate gene-gene interactions with *HPC1* and other loci.

Analysis of white families stratified by median age was also then restricted to families with 5 or more affected men (Table G-1). Older-onset densely-affected families (median ages 65-59 and 70+ years) had positive NPL scores at all *HPC1* markers, while younger-onset densely-affected families had NPL scores < 0 at most markers. A peak multipoint lod of 1.05 and NPL of 1.16 (p=0.13) were seen at D1S1660 among 11 families with median age $\geq$ 70 years and 5 or more affected men. These results may indicate that the large families with the most power contribute to the suggestive *HPC1* results in older-onset families.

Grade. White families were classified according to the tumor grade of affected men as follows: 48 families with only low or both low and moderate grade tumors, 58 families with only moderate grade tumors, and 37 families in which at least one affected man had a high-grade tumor. Results are presented in Table 2-6. In all family groups, some *HPC1* markers were positive at high values of θ . In 37 families with at least one

high-grade case, multipoint analysis assuming heterogeneity produced Hlods of 0.21 and 0.08 at markers D1S2818 and D1S2818, respectively. A peak NPL score of 1.14 (p-value=0.13) was seen at marker D1S2818 in this group. When the analysis was restricted to families with minimal evidence for linkage to other loci, 16 families with at least one case of high-grade disease produced positive 2-point lod scores at all markers and NPL scores > 0.60 with a peak NPL score of 2.03 (p = 0.03) at marker D1S2818 (Table 2-6). Additionally, 26 families with only moderate grade disease and minimal evidence for other linkage produced NPL scores > 0.86 at all markers (peak NPL = 1.42, p=0.08). Because NPL scores remain negative among families with a mixture of low and moderate grade disease after consideration of other linkage, these results may indicate an effect of *HPC1* among moderate and high grade disease.

When white families with at least one high-grade were further stratified by median age at diagnosis (< 65 years, 65+ years) an interesting difference is observed between the groups (Table G-2). NPL scores were negative at all markers for the younger onset group and positive at all markers for the older onset group. In 27 "high-grade" families with median age at diagnosis $\geq$ 65 years, a peak NPL of 1.98 (p=0.03) was seen at D1S2818 (multipoint Hlod = 1.04). Analysis of 10 families in this older-onset, high-grade group that had 5 or more affected men revealed a peak NPL of 2.05 (p=0.04) at D1S2127 (multipoint Hlod = 1.43). This difference by median age was also seen among the families with only moderate grade, though there is less suggestion of linkage in this group in general; the peak NPL was 1.21 (p=0.12) at D1S1660 for 31 families with median age > 65 years and moderate grade only (Table G-2).

Stage. Results for white families classified by stage are presented in Table 2-7. The highest 2-point lod scores for *HPC1* markers were seen in the group of 55 families having local and regionally spread cancers, with peak lods of 0.35 ($\theta = 0.14$) at D1S2818 and 0.83 ($\theta = 0.08$) at D1S1660. When families having lod scores > 0.1 at D1S407, D1S2785, and DXS984 were excluded, a trend in NPL scores by stage was observed (Table 2-7). Forty families with all local stage produced negative NPL scores at all *HPC1* markers (p-values 0.62-0.82), 25 families with local and regional stage cancers produced positive NPL scores ranging from 0.11 to 0.99 (p-values 0.15-0.44), and 12 families with at least one high stage case produced NPL scores > 1.77 and p-values less than 0.05 at all markers (p-values 0.01-0.04).

Families were further stratified by median age at diagnosis (Table G-3). Among 16 families with median age at diagnosis $\geq$ 65 years and at least one man with advanced stage disease, NPL scores for *HPC1* markers ranged from 0.93 to 2.11 (p-values 0.03 to 0.17) (Table G-3), while the younger-onset families had NPL scores < -1.24 at all *HPC1* markers. Analysis of 6 families with median age at diagnosis $\geq$ 65 years, at least one man with advanced stage disease, and 5 or more affected men, a peak NPL of 2.26 (p=0.03) at D1S2127.

Aggressive Disease. Aggressive disease was defined to describe a prostate cancer case with either high grade disease or regional or distant disease (see methods). Families were then stratified by the percent of aggressive disease among affected men; results of *HPC1* analyses are presented in Table 2-8. Assuming heterogeneity, positive Hlods were seen for 59 families with at least one but less than half of affected men

having "aggressive disease", with a peak multipoint Hlod of 0.32 (α = 0.27) at marker D1S2818 (NPL = 1.10, p-value = 0.14). Removal of families potentially linked to *PCaP*, or *HPCX*, or *CAPB* revealed positive NPL scores at all *HPC1* markers among 27 families with at least one case with "aggressive disease" (Table 2-8). Twenty-seven remaining families with at least one but less than half "aggressive disease" cases had NPL scores > 0.97 (peak NPL = 1.74, p = 0.047 at D1S2818), and 31 families with more than half "aggressive disease" cases had NPL scores > 0.36 at all markers (peak NPL = 1.38, p = 0.089 at D1S518).

Analysis stratified by median age at diagnosis revealed that older onset families ($\geq$ 65 years) with $\geq$ 50 percent aggressive disease cases may contain more *HPC1* linked families than younger onset families (< 65years) (Table G-4). Multipoint lod scores and NPL scores were negative among the older-onset group (10 families) and ranged from 0.39 to 1.75 (p-values 0.05 – 0.34) in the younger onset group (16 families). Seven older-onset families with 5 or more affected men and $\geq$ 50 percent aggressive disease cases produced a peak NPL of 2.90 (p=0.009) at marker D1S518 (Table G-4).

Year of Diagnosis. Families were classified by the most recent year of diagnosis of affected men, and results of *HPC1* linkage analysis are presented in Table 2-9. In contrast to one study (Xu et al., 2000), analysis of these 3 families with men all diagnosed before 1990 did not yield any evidence for linkage. Negative lod, Hlod, and NPL scores were seen at all *HPC1* markers. Analysis of families with men diagnosed in later years, showed the most evidence for linkage in families with men diagnosed as recently as 1996-1999. In this group of 24 families, a maximum 2-point lod score of 0.50

(θ =0.14) was seen at D1S1660 and a peak NPL of 1.55 (p=0.07) was observed at D1S518 (Table 2-9).

Analysis of *PCaP*

All Families. In the pooled dataset, there was no significant evidence for linkage to *PCaP* markers in the 1q42.2-43 region (Table 2-10), however the data were consistent with a linked subset. Using Model B+, 2-point lod scores peaked at a lod of 0.57 (θ= 0.26) at marker D1S2785. Multipoint analysis, assuming heterogeneity, produced a peak Hlod of 0.50. Analysis of the 149 families using the two models considered in the original finding of *PCaP* linkage showed the same trend of results as well. When 71 families that had lod scores > 0.1 at *HPC1*, *HPCX*, and *CAPB* markers were excluded, results were similar, with negative multipoint lod and NPL scores (Table 2-10).

Median Age. When white families were stratified by median age at diagnosis of sampled affected men, the youngest onset families had the most evidence for linkage to *PCaP* makers (Table 2-11). The group of 13 families with median age at diagnosis < 60 years produced positive 2-point lod scores at markers D1S2785, D1S547, and D1S1609 (peak lod = 0.90, θ = 0.00 at marker D1S2785). Multipoint analysis assuming heterogeneity revealed positive Hlods and NPLs at these markers as well, with a maximum Hlod of 0.42 and a peak NPL score of 0.79 (p=0.21) at D1S1609. When families with potential evidence for linkage at other loci were removed, a trend by median age at diagnosis was observed. Families with median age < 60 produced NPL

scores > 1.1 at most markers, families with median age 60-64 have NPL scores between 0.33 and 0.73, and families with older median ages had negative NPL scores (Table 2-11). All NPL scores were > 0.11.

Restricting this analysis to families with 5 or more affected men did not show the same trend of stronger results in families with younger median age (Table H-1). Multipoint lod scores were similar across age groups, and NPL scores were negative for 4 families with median age < 60 years and 5 or more affected men. A peak NPL of 1.24 (p=0.11) was seen among 20 families with median age of diagnosis 60-64 years and 5 or more affected men at D1S1609 (Table H-1).

Grade. Analysis was conducted stratifying white families by distribution of tumor grade (Table 2-12). In all family groups, 2-point lod scores at *PCaP* markers become positive at high values of θ for most markers. Multipoint analysis assuming heterogeneity revealed positive Hlods for most markers for 58 families with all moderate grade cancer and 37 families with at least one high-grade cancer. When families with evidence for other linkage were removed, peak 2-point Hlods of 0.50 (θ =0.12) and 0.42 (θ =0) were seen at markers D1S547 and D1S1609, respectively, in 32 remaining families with all moderate grade cancers. In this group, most NPL scores were positive (peak NPL = 1.03, p=0.15 at D1S1609), while all NPL scores were negative in families with low and moderate grade cancer or at least one high-grade cancer (Table 2-12).

Ten families with at least one high-grade case and median age >= 65 years and 5 or more affected men produced positive multipoint lod scores, Hlods, and NPL scores (Table H-2). A peak NPL of 2.29 (p=0.03) was seen at marker D1S547. NPL scores

were negative in 27 families with at least one high-grade case and median age >= 65 years (Table H-2).

Stage. White families were stratified according to the stage at affected mens' prostate cancer diagnosis (Table 2-13). Two-point lod scores were positive at all *PCaP* markers for families with at least one man with distant stage disease and were negative at all markers for families with only local stage disease. Multipoint analysis revealed positive Hlod scores at all markers among families with at least one advanced stage case and negative at all *PCaP* markers for the other family groups. A peak NPL of 0.91 (p=0.18) was seen among 25 families with at least one advanced stage case. This trend by tumor grade was not seen after removing families with evidence for linkage to other loci. The only positive NPL scores in the remaining families were seen in 26 families with local and regional staged markers D1S2785, D1S547, and D1S1609 (peak NPL=0.92, p=0.18) (Table 2-13).

Families were then stratified by median age at diagnosis and number of affected men. No clear trends in *PCaP* linkage by tumor grade and these characteristics were revealed (Table H-3). Six families with at least one advanced stage case and median age $\geq$ 65 years and 5 or more affected men produced peak NPL scores > 1.22 at markers D1S2785, D1S547, and D1S1609 (p-values 0.10-0.12) (Table H-3).

Aggressive Disease. Table 2-14 shows results for *PCaP* analyses stratified by the amount of aggressive disease in each family (no cases, < 50 percent of cases, and $\geq$ 50 percent of cases). Positive NPL scores were only seen among 59 families with at

least one but < 50 percent of cases (peak NPL = 0.48, p=0.35). Similar results were seen when families with potential evidence for other linkage were removed (Table 2-14).

Analysis of families further stratified by median age at diagnosis and number of affected men, showed that 18 families with median age ≥ 65 years, 5 or more affected men, and at least one but < 50 percent of cases of aggressive disease had a peak NPL of 1.97 (p=0.04) at D1S1609. No clear trends in *PCaP* linkage by aggressive disease and median age of diagnosis and these characteristics were revealed (Table H-4).

Analysis of *HPCX*

All Families. In the pooled dataset, there was no evidence for linkage to *HPCX* markers, with negative multipoint lod and Hlod scores at all 8 *HPCX* markers (Table 2-15) using Model B+. One NPL score was positive, however, for marker DXS984 (NPL = 0.40, p=0.34). When 71 families were excluded that had lod scores > 0.1 at *HPC1*, *PCaP*, or *CAPB* markers, a maximum 2-point lod score assuming heterogeneity was seen at DXS984 (θ =0.00, α =0.36) (Table 2-15). Multipoint analysis revealed a positive Hlod of 0.14 (α =0.25) at DXS984. NPL scores at all markers were insignificant, though they were positive at DXS984, DXS1193, and DXS8069 (peak NPL = 0.76, p=0.22, DXS984).

Mode of Inheritance. Because of *HPCX* resides on the X chromosome, the pattern of disease transmission in linked families would reflect that a disease allele at *HPCX* could only be passed from mother to child. Therefore, for this analysis, white families were also stratified by putative inheritance pattern: affected father and son or

prostate cancer on paternal side only would indicate father to child transmission ("male-to-male"); no affected father and son or prostate cancer on maternal side would be consistent with X-linked inheritance ("not male-to-male"); and prostate cancer in one sibship only does not indicate a certain mode of inheritance ("siblings only"). Multipoint analysis revealed positive NPL scores at several *HPCX* markers in 82 families with male-to-male transmission of disease, and negative lod scores in the other groups, including the joined group of no male to male transmission (Table 2-16). Removing families with evidence of linkage to other loci produced different results. NPL scores were negative at all markers among the male-to-male group and among siblings only, but positive at all markers among the not male-to-male group (Table 2-16). Among 7 remaining families in the not male-to-male group, a maximum NPL score of 0.61 (p=0.26) was seen at DXS984. Combining these families with the remaining 29 families having affected siblings only revealed only one positive NPL score of 0.25 (p=0.39) at DXS984 (Table 2-16).

The *HPCX* analysis by mode of transmission was further stratified by median age of diagnosis and number of affected men. Results are presented in Table I-1. No clear trend in age at diagnosis and mode of disease transmission seemed apparent. In the "siblings only" group, however, families with 5 or more affected men produced NPL scores > 1.00 at different markers according to median age at diagnosis. Two families of affected siblings with median age of diagnosis < 65 years and 5 or more affected men produced NPL of 1.01 (p=0.20) at DXS984, and 5 families of affected siblings with median age of diagnosis $\geq$ 65 years and 5 or more affected men produced an NPL score

of 1.21 (p=0.11) at DXS1200. The very small number of families in these groups make the results difficult to interpret.

Median Age. When white families were stratified by median age at diagnosis of sampled affected men, the highest 2-point lod scores at *HPCX* markers were seen in the group of families with median age at diagnosis between 60 and 64 years, with a peak lod of 0.79 (θ =0.10) at marker DXS984 (Table 2-17). Assuming heterogeneity, this increased to an Hlod of 1.02 (θ = 0). Multipoint analysis revealed positive NPL scores at all markers in this 60-64 year median age group with a peak NPL of 1.28 (p=0.11) at DXS984. When families with potential evidence of linkage at other loci were removed, peak lod scores of 1.14 (θ = 0) at D1S1193, 0.69 (θ =0) at DXS8103, and 0.67 (θ =0.12) at DXS8103 were seen in this group. In other age groups, only a few lod scores became positive at high values of θ . However, multipoint analysis of families with minimal evidence of other linkage revealed several NPL scores > 1.0 in the < 60 years and 60-64 years median age groups (Table 2-17). A peak NPL of 1.63 (p=0.13) was observed among 3 families with median age < 60 years and minimal evidence of other linkage.

Restricting analysis to white families with 5 or more affected men revealed NPL scores > 1.10 in the youngest and oldest median age groups (Table I-2). Among 4 families with median age at diagnosis < 60 years and 5 or more affected men, a peak NPL of 1.34 (p=0.13) at marker DXS6806 and positive NPL scores in the centromeric region of *HPCX*.were observed. Among 11 families with median age at diagnosis $\geq$ 70 years and 5 or more affected men, a peak NPL of 1.33 (p=0.10) at marker DXS297 and positive

NPL scores in the non-centromeric region of *HPCX*. These results may provide support for the large *HPCX* region containing two loci (Table I-2).

Grade. Analysis was conducted stratifying white families by distribution of tumor grade (Table 2-18). Two-point lod scores for *HPCX* markers became slightly positive at high values of θ in 37 families with at least one high-grade case, and a peak 2-point lod score of 0.48 (θ =0.18) was seen at DXS984. Forty-eight families with low and moderate grade cancers had negative lod and Hlod scores at all markers except DXS1200 with an Hlod of 0.05 (θ =0.18, α = 0.43). Multipoint analysis of this family group showed negative Hlods and NPL scores at all *HPCX* markers, except at DXS984 (NPL= 0.53, p=0.29). A peak NPL score of 0.54 (p=0.29) at DXS1200 was observed among 58 families with all moderate grade cases. Exclusion of families with potential linkage to other loci, produced peak 2-point lod scores of 0.66 (θ =0.00) at DXS1193 and 0.65 (θ =0.08) at DXS984 in families with at least one high-grade case (Table 2-18). Peak multipoint results, however, occurred among 29 families with low and moderate grade cancers and with minimal evidence of other linkage at marker DXS984 (NPL = 1.11, p = 0.13).

The analysis was further stratified by median age at diagnosis and number of affected men, and results are presented in Table I-3. Among families with moderate grade disease only, those with median age at diagnosis < 65 years and 5 or more affected men produced a peak NPL of 1.35 (p=0.09) at marker DXS6806 and positive NPL scores in the centromeric region of *HPCX*. Analysis of 7 families at least one high-grade case, median age at diagnosis $\geq$ 65 years, and 5 or more affected men revealed a peak 2-point

lod score of 1.55 (θ =0) with an NPL of 1.05 (p=0.15) at marker D1S984. At the more distal region, as well, NPL scores > 1.0 were observed with a peak NPL score of 1.35 (p=0.10) at marker DXS1193 (Table I-3).

Stage. White families were stratified according to the stage at diagnosis of affected mens' prostate cancer. Two-point analysis revealed slightly positive lod scores for *HPCX* markers at high values of θ for 63 families with all local stage disease (Table 2-19). Non-parametric multipoint analysis revealed negative NPL scores in this group at all markers except DXS984 (NPL=0.77, p=0.22). Among 25 families with at least one case of distant stage cancer however, NPL scores were > 0.25 at all markers except DXS984 (p-values 0.27-0.54) (Table 2-19). Removing families with evidence for potential linkage to other loci resulted in a peak 2-point Hlod of 0.50 (θ =0.02, a=0.63) and a peak NPL score of 1.00 (p=0.16) at DXS984 among families with all local stage. Among 14 families with at least one distant stage cancer and minimal evidence for other linkage, all multipoint Hlods and NPL scores were positive (peak NPL=0.81, p=0.20 at DXS1200) (Table 2-19).

Analysis of families further stratified by median age at diagnosis and number of affected men revealed the strongest results among 6 families with local and regional stage disease, median age at diagnosis < 65 years, and 5 or more affected men (Table I-4). NPL scores > 1.50 were seen at 6 markers throughout the *HPCX* region with a peak NPL of 1.71 (p=0.05) at marker DXS1193. No clear trends in *HPCX* linkage by stage and median age of diagnosis were revealed.

Aggressive Disease. Families were stratified by the amount of "aggressive disease", and results of *HPCX* analyses are presented in Table 2-20. The highest 2-point lod score was achieved at marker DXS8069 (lod=0.37, θ =0.12) for 59 families with at least one but less than half of cases with "aggressive disease". Multipoint analysis revealed several positive NPL scores in this family group, with a peak NPL of 1.08 (p=0.14) at DXS984. Among 5 families with only aggressive disease, NPL scores were greater than 1.09 (p=0.23) at markers DXS1200, DXS297, DXS1193, DXS8069, and DXS8103 (Table 2-20). Removal of families with evidence of linkage to other loci resulted in peak 2-point lods of 0.69 (θ =0.00) at DXS8103, 0.47 (θ =0.00) at DXS1193, and 0.33 (θ =0.00) at DXS8069 in the group of families with 50 percent of more affected men with aggressive disease. Many multipoint lods and all multipoint Hlods were positive in this family group, though NPL scores remained insignificant in all family groups (Table 2-20).

Analysis of families further stratified by median age at diagnosis and number of affected men revealed the NPL scores > 1.26 among families with 5 or more affected men with 50 percent or more cases with aggressive disease among both younger- and older- onset families (Table I-5). Among 5 such families with median age of diagnosis < 65 years, a peak NPL of 1.31 (p=0.10) was seen at marker DXS1193, and among 7 such families with median age of diagnosis $\geq$ 65 years, a peak NPL of 1.44 (p=0.09) was seen at marker DXS297. No clear trends in *HPCX* linkage by aggressive disease and median age of diagnosis were revealed.

Analysis of *CAPB*

All Families. Results of analysis in the *CAPB* 1p36 region are shown in Table 2-21. In the pooled dataset, 2-point lod scores using Model B+ peaked to 0.16 ($\theta = 0.30$) and 0.86 ($\theta = 0.18$) at D1S1597 and D1S407, respectively. Multipoint analysis revealed positive Hlods and NPL scores at both markers with an estimate of 15 percent to 18 percent of the 149 families being linked. Analysis was repeated excluding families that had evidence of linkage to other loci (lod $\geq$ 0.1 at D1S518, D1S2785, and DXS984). Analysis of the remaining 78 families yielded multipoint lod scores of 0.35 (D1S1597) and –0.23 (D1S407) and NPL scores of 2.05 (p=0.023) and 1.98 (p=0.027) at D1S1597 and D1S407, respectively (Table 2-21).

Median Age. When white families were stratified by median age at diagnosis of sampled affected men, the highest 2-point lod scores of 0.75 ($\theta = 0.10$) and 0.81 ($\theta = 0.10$) were seen in the group of 34 families with median age between 60 and 64 years at markers D1S1597 and D1S407, respectively (Table 2-21). This family group also had positive multipoint lod, Hlod, and NPL scores (NPL = 1.36 and 1.35, p = 0.09). Forty-two families with median age $\geq$ 70 years produced negative lod scores, but positive NPL statistics of 1.45 and 1.54 at D1S1597 and D1S407 respectively. Analysis stratified by median age was repeated, excluding families with marginal evidence for linkage to *HPC1*, *PCaP*, or *HPCX*. The highest 2-point lod score was seen in the youngest onset group (5 families with median age < 60 years) with lod = 0.47 ($\theta = 0$) at D1S1597 (Table 2-21). This group also had positive multipoint lod and Hlod scores and NPL scores > 0.73. In 15 families with median age between 60 and 64 years that didn't have evidence

of other linkage, lod scores were consistently positive and NPL scores were increased (NPL = 1.74, p = 0.05 at D1S1597; NPL = 1.62, p = 0.06 at D1S407).

The analysis was further stratified by median age at diagnosis and number of affected men, and results are presented in Table J-1. Twelve families with 5 or more affected men and median age of diagnosis 60-64 years produced NPL scores were 1.41 (p=0.09) and 1.46 (p=0.08) at D1S1597 and D1S407, respectively. Analysis of 11 families with 5 or more affected men and median age of diagnosis $\geq$ 70 years revealed NPL scores of 0.30 (p=0.35) and 0.46 (p=0.30) at D1S1597 and D1S407, respectively (Table J-1).

Grade. In the 49 families with both low and moderate grade tumors, the maximum 2-point lod score for *CAPB* markers was 0.26 (θ = 0.18) at D1S407 (Table 2-21). In the 37 families having at least one case with a high-grade tumor, positive 2-point and multipoint lod scores were observed. Multipoint Hlods were greater than 0.55 and NPL scores produced p-values < 0.05 (NPL=1.82 p = 0.04 at D1S1597; NPL=1.83 p = 0.04 at D1S407). Families were excluded if they had possible linkage to another locus, and the remaining families seemed to produce a trend in 2-point lod scores by grade (Table 2-21). Twenty-seven families with only low and moderate grade cancers had negative lod scores at all θ s for D1S1597 and D1S407. Thirty-one families with moderate grade cancers only produced peak positive lod scores at θ = 0.22 at both markers (lod = 0.10 at D1S1597 and lod = 0.08 at D1S407). Seventeen families with at least one high-grade cancer produced peak lod scores at θ = 0 of 1.24 for D1S1597 and 0.77 for D1S407. Multipoint analysis, assuming heterogeneity, showed a similar trend,

culminating in Hlod scores of 1.58 (D1S1597) and 1.42 (D1S407) in families with at least one high-grade cancer. NPL scores of 2.44 (D1S1597) and 2.34 (D1S407) provided p-values of 0.01 in this family group.

The analysis was further stratified by median age at diagnosis and number of affected men. Analysis of 38 families with median age $\geq$ 65 years and low and medium grade disease revealed NPL scores of 1.30 (p=0.10) and 1.22 (p=0.11) for D1S1597 and D1S407 respectively (Table J-2). When families with at least one high-grade cases were subdivided by median age (< 65 years/$\geq$ 65 years), NPL scores > 1.22 were seen at both markers in each group (Table J-2).

Stage. White families were classified according to the stage at affected mens' prostate cancer as follows: 63 families with only locally-confined cancers (Stage A or B), 55 families with at least one regionally spread cancer (Stage C), but no distant metastasis, and 25 families in which at least one affected man had cancer with distant metastasis (Stage D). Positive two-point lod scores for *CAPB* markers were seen at high values of θ in the group of families having local and regionally spread cancers, with peak lods of 0.27 (θ = 0.24) at D1S1597 and 0.12 (θ = 0.28) at D1S407. Multipoint lod scores were negative for all family stage groups, however, assuming heterogeneity, lod scores became slightly positive in the groups with local and regional disease and at least one advanced stage disease. The highest NPL scores were observed in the group of families with local disease only (NPL= 0.97, p = 0.17 at D1S1597 and NPL= 1.15, p = 0.13 at D1S407). When families with evidence of linkage to another locus were excluded, multipoint Hlods became positive for the 39 families with local stage only and 22

families with local and regional stage (Table 2-21). NPL scores in these family groups were > 1.31 and p-values were < 0.10.

The analysis was further stratified by median age at diagnosis and number of affected men. Ten families with median age < 65 years and at least one advanced stage case produced NPL scores of 1.30 (p=0.10) and 1.14 (p=0.12) at D1S1597 and D1S407, respectively (Table J-3). Further restriction to 6 families with 5 or more affected men produced NPL scores of 1.49 (p=0.07) and 1.46 (p=0.08) at D1S1597 and D1S407, respectively.

Aggressive Disease. The prostate cancer families stratified were based on the number of cases of "aggressive disease" (grade III or Stage C or D cancer). None of the family subgroups based on amount of "aggressive disease" (none, < 50 percent of cases, or >= 50 percent of cases) provided significant evidence for linkage to *CAPB* markers, though each group had positive 2-point lod scores at high values of θ (Table 2-22). Negative multipoint lod scores were seen in all 3 family groups; however, when further limited to 5 families having all affected men of "aggressive disease" positive multipoint lod scores 0.13 and 0.14 were seen at D1S1597 and D1S407, respectively. Assuming heterogeneity, a trend of increasing multipoint lods, α 's, and Hlods was observed from families with no "aggressive disease" cases to families with < 50 percent of cases to families with 50 percent or greater. This trend however, was not seen in nonparametric multipoint analysis. Families were excluded if they had possible linkage at another loci, and 15 remaining families with 50 percent or more affected men with "aggressive disease" had positive 2-point lod scores at θ = 0 (Table 2-22). This may be

due to the removal of one family having all cases of "aggressive disease" that had evidence for linkage to other loci.

The analysis was further stratified by median age at diagnosis and number of affected men. When families with 50 percent or more cases with aggressive disease were subdivided by median age, 10 families with median age < 65 years produced NPL scores of 1.55 (p=0.07) and 1.70 (p=0.05) at D1S1597 and D1S407, respectively (Table J-4). Further restriction to 6 families with 5 or more affected men produced NPL scores of 1.87 (p=0.05) and 2.09 (p=0.03) at D1S1597 and D1S407, respectively. Though a small number of families in this group were analyzed here, these results indicate that multiply-affected families with aggressive disease diagnosed at young ages may have linkage to *CAPB*.

Discussion

It is clear that multiple genetic loci are involved in hereditary prostate cancer. To date, five putative susceptibility genes (thought to be rare and highly penetrant) have been identified by linkage analyses of high-risk prostate cancer families. To facilitate both the positional cloning of these loci and the identification of additional loci, analysis of independent datasets is necessary. Because of the known genetic heterogeneity of prostate cancer, confirmatory analyses should include examination of evidence for linkage to known loci and clinical characteristics thought to be genetically determined. While age at diagnosis and race have been utilized previously in confirmatory prostate cancer analyses, this study is the first to consider multiple loci and specific clinical data.

The hypothesis that hereditary prostate cancer may differ from non-inherited disease has been investigated previously. Previous studies have compared clinical characteristics of affected men with differing types of family history: 1) no family history (sporadic), 2) some family history (familial), and 3) family history of a particular pattern (3 or more affected relatives in a nuclear family, in 3 or more generations, two relatives affected < 55 years; hereditary) (Carter et al., 1993). Numerous studies have shown that familial or hereditary cases tend to be diagnosed at younger ages than sporadic cases (Carter et al., 1993; Bastacky et al., 1995; Keetch et al., 1996; Bauer et al., 1998; Bratt et al., 1998; Norrish et al., 1999). Two studies of prostatectomy specimens found that most pathological features were similar (which would be expected because of the use of data only from men who had undergone radical prostatectomy), except that the hereditary or familial tumors were of lower grade than the sporadic tumors (Bastacky et al., 1995; Keetch et al., 1996). Bastacky et al, (1995) studied 81 men who had undergone radical prostatectomy, and observed lower grade in men with familial disease and hereditary disease than sporadic ($p = 0.0001$). Keetch et al. (1996) studied tumor differentiation of 100 radical prostatectomy specimens and found lower Gleason score in hereditary (mean = 5.6) cases than sporadic (mean = 6.2) cases ($p = 0.008$). In an Australian population-based study, incident cases with familial prostate cancer had a lower proportion of regionally-spread disease than sporadic cases ($p=0.009$) (Norrish et al., 1999). Other family history studies show no significant difference in any clinical variable other than age at diagnosis (Carter et al., 1993; Bauer et al., 1998; Bratt et al., 1998). Two analyses have shown that affected men with a family history of prostate cancer have lower five-year biochemical relapse-free survival rates ($p< 0.001$),

suggesting that familial prostate cancer may have a more aggressive course than nonfamilial prostate cancer (Kupelian et al., 1997a; Kupelian et al., 1997b).

Two analyses of high-risk prostate cancer families have examined clinical characteristics. In one study, 74 North American families that were part of the dataset originally showing evidence for *HPC1* linkage were analyzed (Smith et al., 1996; Grönberg et al., 1997b). Families were classified as "potentially-linked" (33 families) or "potentially-unlinked" (41 families) based on whether all affected men in a family shared an *HPC1* haplotype (Grönberg et al., 1997b). Though linkage in each family can not be truly confirmed until *HPC1* is cloned and mutations are shown to be transmitted, the authors concluded that mean age at diagnosis was significantly lower in potentially-linked families than potentially-unlinked families (63.7 years v. 65.9 years). High-grade cancers were more common in potentially-linked families than potentially-unlinked families (39 percent v. 29 percent, $p = 0.04$) (Grönberg et al., 1997b). However, interpretation of these results is difficult, because a trend towards higher-grade tumors in potentially-linked families was not seen (potentially-linked families also had more low-grade tumors) (Laniado, 1998). The authors also concluded that cancers that had spread beyond the prostate or metastasized to distant sites (Stage C or D) were more common in potentially-linked families than potentially-unlinked families (41 percent v. 31 percent) (Grönberg et al., 1997b). This study was the first to consider the relationship between clinical characteristics and evidence for linkage to a particular putative prostate cancer loci. It may indicate characteristics of families likely to be linked to *HPC1* and facilitate explanations of the discrepant *HPC1* linkage results between studies. Additionally, Witte et al. (2000) conducted a prostate cancer sib-pair linkage analysis considering disease as a

quantitative trait using Gleason score (range 2-10). They found several regions of interest, including some linkage near the *CAPB* region ($p < 0.01$) indicating that *CAPB* may be involved in high-grade disease (Witte et al., 2000).

In the current study, a total of 149 high-risk prostate cancer families were analyzed at 4 putative susceptibility loci (*HPC1* at 1q24-25, *PCaP* at 1q42.2-43, *HPCX* at Xq27-28, and *CAPB* at 1p36) incorporating data from the medical records of 505 affected men. In an effort to define genetically homogeneous family groups, families were stratified by race, median age at diagnosis, distribution of tumor grade, distribution of cancer stage, distribution of aggressive disease, assumed transmission pattern of disease, and evidence for linkage to other loci. Our goal was to create family groups with similar clinical characteristics in order to explore if any characteristic may describe families with evidence of linkage to one of 4 loci.

Two-point and multipoint parametric lod scores were produced, first under homogeneity, then assuming heterogeneity regardless of whether there was significant evidence of linkage, and multipoint non-parametric linkage (NPL) was also performed. Lod score analysis allows for the maximum likelihood estimation of the recombination fraction (θ) between a disease gene and a genetic marker and is the most powerful method when most parameters describing the genetic model of disease are correctly specified (Clerget-Darpoux et al., 1986; Xu et al., 1998a). Lod score analyses which assumed specific models of prostate cancer inheritance was used to identify each locus considered here in at least one study (Smith et al., 1996; Berthon et al., 1998; Xu et al., 1998b; Gibbs et al., 1999a). Because the true genetic model of prostate cancer will

remain unknown until the cloning and characterization of genes, NPL scores (which don't require the specification of these parameters) may also serve as a useful indicator of evidence for linkage.

We have previously reported that in this dataset as a whole, there was no significant evidence for linkage to *HPC1* markers in the 1q24-25 region (McIndoe et al., 1997; Goode et al., 2000). In the current analysis of *HPC1*, it appears that white families in this dataset having median age at diagnosis > 70 years may have the strongest evidence for *HPC1* linkage with multipoint Hlod scores reaching 0.95 and NPL scores reaching 1.59 (p=0.06). When families with possible evidence of other linkage, were removed positive NPL scores were seen in both the 65 –69 year and > 70 year median age group, while negative NPL scores were seen in the younger onset groups. When families were stratified by tumor grade and cancer stage, evidence for linkage remained stronger, for the most part, among older onset than younger onset families. These results were unexpected because epidemiologic studies and segregation analyses predict that hereditary cases are more likely to be diagnosed at younger ages (Cannon et al., 1982; Carter et al., 1992), and, more particularly, because other research groups (including the combined analysis of 772 families) have found that evidence for *HPC1* linkage is provided primarily by families with a younger mean age at onset (Grönberg et al., 1997b; Grönberg et al., 1997c; Grönberg et al., 1999; Neuhausen et al., 2000; Xu, 2000).

It is useful to consider possible explanations for the suggestion of *HPC1* linkage among older onset families, keeping in mind that this result is not significant. The estimates of median and mean age at diagnosis did not include data on deceased affected

men (only men self-reporting age), therefore, older-onset families studied here, may in fact not be older onset, because the men diagnosed at younger ages who would have brought the median age down are deceased (men diagnosed at younger ages have poorer survival). However, recalculation of median age at diagnosis in families with extreme median ages (< 60 years or >= 70 years) and 2 or more deceased affected men when the age of diagnosis of these affected men reported by first degree relatives was included, did not change the estimates of median age of diagnosis for the majority of these families. The use of median (as opposed to mean) to describe age at diagnosis does not account for the difference in our results compared to other groups; in fact, we have previously reported positive NPL scores in older onset families when stratified by mean age (Goode et al., 2000). Differences in the genetic model assumed are not responsible for the discrepancy either, because both parametric and non-parametric results are stronger in our older onset families. False positives can result from incorrect specification of marker allele frequencies, which are considered only when founders are not genotyped (Ott, 1992; Ott, 1999). If fewer founders are genotyped in the older onset families, this may increase the probability of false positive results in this group; however the number of ungenotyped founders did not vary by median age of families in this dataset. The role of *HPC1* in determining susceptibility, age at diagnosis, or progression of prostate cancer must be further clarified.

Additionally, there was some suggestion from this analysis that *HPC1* may be involved in high-grade disease. Sixteen white families with at least one high-grade case and with minimal evidence for linkage to other loci (lod < 0.10 at *PCaP*, *HPCX*, and *CAPB*) produced a peak NPL score of 2.03 (p = 0.03) at marker D1S2818. A trend was

observed in that families of men with only moderately differentiated disease also had positive NPL scores, while families with only low or both low and moderate grade disease had negative results. These findings are consistent with the study comparing *HPC1* "potentially-linked" and "potentially-unlinked" families (Grönberg et al., 1997b).

Results at *HPC1* may also indicate an involvement in advanced stage disease. Analysis of 12 white families having at least one man with distant prostate cancer metastases and minimal evidence for linkage to other loci yielded NPL scores > 1.77 (p-values < 0.05) at all *HPC1* markers. Though only 3 families in this group of 12 were also in the group of 16 families with high-grade disease, it is important to consider that stage and grade are correlated. In the current dataset, grade and stage classifications for families were not independent (Fisher's exact p = 0.005); for instance, families with low and moderate grade disease tended to be classified in the group of families with only localized stage (Table F-4). In an attempt to encompass both grade and stage data into "aggressive disease" we stratified families by the percent of affected men with either high-grade disease or cancer that had spread beyond the prostate or metastasized to a distant site (Stage C or D). There was some evidence that *HPC1* may be involved with aggressive disease. In particular, 7 white families with at least half of the cases with aggressive disease, with median age at diagnosis $\geq$ 65 years, and 5 or more affected men produced a peak NPL of 2.90 (p=0.009) at marker D1S518. These findings may also lend support to the study that compared *HPC1* "potentially-linked" and "potentially-unlinked" families (Grönberg et al., 1997b). However, the fact that in the current dataset, families with *older* age at diagnosis have the most evidence for linkage to *HPC1* while in

other datasets more evidence for linkage appears in families with *younger* ages at diagnoses leaves these results difficult to interpret.

A combined analysis of linkage to *HPC1* assessed 772 high-risk prostate cancer families from 9 research groups including the 149 families analyzed here (Xu, 2000). This type of large pooled analysis has increased power to examine linkage and heterogeneity for a complex disease such as prostate cancer. Analysis of the combined dataset revealed a peak multipoint Hlod of 1.40 ($p = 0.01$) at D1S212 and estimated that 6 percent of families were linked (1-lod support interval 0.01-0.12) (Xu, 2000). Families were stratified by several characteristics, and the most evidence for linkage was observed among families with male-to-male transmission (to remove potentially X-linked families), mean age at diagnosis < 65 years, and 5 or more affected men (peak multipoint Hlod = 2.25, $p=0.001$). Overall, this study found that linkage to *HPC1* among high-risk families is much less than originally estimated (Smith et al., 1996; Xu, 2000). Analyses of pooled datasets at the other putative prostate cancer susceptibility loci may be informative in this way, as well.

In this dataset as a whole, there was no significant evidence for linkage to *PCaP* markers in the 1q42.2-43 region, however the data were consistent with a linked subset, as we have shown previously (Gibbs et al., 1999a). The original report of *PCaP* linkage showed the most evidence for linkage among families with age at diagnosis < 60 years in the youngest generation of affected men (Berthon et al., 1998). Weak support for an age of onset effect on strength of linkage results was observed in the current dataset as well. Analysis of 13 white families with median age < 60 years revealed a peak Hlod of 0.42

and a peak NPL score of 0.79 (p=0.21) at D1S1609. When families with potential evidence for linkage at other loci were removed, these values increased to 0.56 and 1.26 (p=0.11), respectively, and a non-significant trend of decreasing multipoint Hlods and NPLs with increasing median age at diagnosis was observed.

We previously analyzed 152 families (including the 149 presented here) and reported negative *PCaP* linkage results among 20 families with mean age of diagnosis < 61 years; NPLs were < 0.15 at 3 markers, and a peak NPL = 0.40 was seen at D1S1609 (p=0.34) (Gibbs et al., 1999a). Eleven families having both median age < 60 years and mean age < 61 years were common to both analyses. Analysis of these 11 families yielded results similar to the analysis of 13 families with median age < 60 years. Various studies of prostate cancer families have defined young age at diagnosis differently, which makes results difficult to interpret. Other groups have not observed evidence for linkage in younger onset families when defined as either two men diagnosed at age < 65 (The ACTANE Consortium, personal communication) or all men in the youngest generation diagnosed at age < 60 years (Whittemore et al., 1999). In the present analysis, the observation of a non-significant trend in median age at diagnosis lends support to the hypothesis of an age effect; younger-onset prostate cancer families may have the most evidence for *PCaP* linkage.

We previously reported a multipoint Hlod of 0.46 and an NPL of 1.22 (p= 0.11) at the *PCaP* marker D1S1609 among families with 5 or more affected men (Gibbs et al., 1999a). An NPL score of 0.30 (p=0.35) was seen in families of this type in another study as well (The ACTANE Consortium, personal communication). Berry et al. (2000)

observed an NPL of 1.45 (p=0.08) in families with mean age at diagnosis < 66 years, at least five affected individuals, and male-to-male transmission (to eliminate potentially X-linked families). In the current stratified analysis of families with 5 or more affected men, it appears that 20 white families with median age of diagnosis between 65 and 59 years may contribute most to our previously reported results (multipoint Hlod=0.69, NPL=1.24, p=0.11). Surprisingly, families with median age < 60 years and 5 or more affected men had negative multipoint results. It is difficult to interpret the suggestions of *PCaP* linkage in younger-onset (median age at diagnosis < 60 years) families and in dense (5 or more affected men) families that may not be present in younger-onset dense families. The small sample sizes of the substratified analyses may be producing spurious results.

Considering additional clinical characteristics, the largest NPL score in the *PCaP* region was seen among 10 white families with median age ≥ 65 years, 5 or more affected men, and at least one high-grade case (NPL=2.29, p=0.03, multipoint Hlod=0.71). This result should not be over-interpreted, however, because no other trend by tumor grade was seen; in fact, NPL scores were negative in the larger group of families with at least one high-grade case and median age ≥ 65 years (not restricting to 5 or more cases per family). Having 5 or more affected men may be the most defining characteristic for potential *PCaP* linkage in families studied here, as reported previously by our group (Gibbs et al., 1999a).

This dataset as a whole did not provide significant evidence for *HPCX* linkage, consistent with our previous analysis of a larger number of families (Peters et al., (in

press)). It is expected that if there were *HPCX* linkage in this dataset, it would be most evident among families without evidence of male-to-male disease transmission. However, stratification by assumed mode of inheritance revealed negative results among families *without* male-to-male transmission and a maximum Hlod of 0.12 and NPL score of 0.84 (p=0.20) among families *with* male-to-male transmission, which was unexpected. Another confirmation study found an NPL of 1.89 (p=0.03) among 43 families with male-to-male transmission (Lange et al., 1999). When families with evidence for linkage to other loci (lod > 0.10) were removed in the current study, analysis of 7 white remaining families with other than male-to-male transmission revealed a maximum 2-point lod of 0.70 and an NPL score of 0.61 (p=0.26) at DXS984. Combining these families with 29 families having affected siblings only (therefore unknown disease transmission) and minimal evidence for other linkage revealed a peak 2-point lod of 0.33 and an NPL score of 0.25 (p=0.39) at DXS984. Lange et al. (1999) observed a peak NPL of 1.51 (p=0.07) among families with no evidence of male-to-male transmission and mean age at diagnosis $\leq$ 65 years. Further stratification of the current dataset by median age of diagnosis did not reveal any clear differences in mode of transmission groups.

Analysis in the *HPCX* region stratified by median age, regardless of mode of transmission suggests that families with younger ages at diagnosis may have some evidence for *HPCX* linkage, when families with lod scores > 0.10 at other loci were removed. A peak NPL of 1.63 (p=0.13) was seen among remaining white families with median age at diagnosis < 60 years, and a peak NPL of 1.45 (p=0.08) was seen among remaining families with median age at diagnosis 60-64 years. Stratification by tumor grade, cancer stage, or aggressiveness of disease did not reveal any clear pattern of

evidence for linkage. Regarding tumor grade, 7 older onset families with at least one high-grade disease with 5 or more affected men produced a 2-point lod score of 1.54 (θ =0.00) at DXS984 and NPL scores > 1.0 at multiple markers. However, the small number of families in each subgroup and the lack of any indication of a trend with aggressive disease make this result difficult to interpret.

The original finding of linkage to *HPCX* was based on analysis of 360 prostate cancer families, obtained through 4 independent research groups based in the United States, Finland, and Sweden (Xu et al., 1998b). In the original dataset as a whole, lod scores maximized at marker DXS1113, but in the Finnish families alone, a maximum lod score was seen at marker DXS1205, which is 10.7 cM away from DXS1113. As discussed in Peters et al. (in press), our current results show lod score peaks at DXS984, which is only 1.4 cM from DXS1205. Some subsets of families, however, show more evidence of linkage to markers near DXS1113. It is possible that there may be two or more loci in the *HPCX* region which segregate in different family collections. Two loci which are in close proximity could appear to be one locus in a linkage analysis. A pooled analysis of multiple datasets at *HPCX* may provide some insight into potential heterogeneity within Xq27-28.

We previously observed evidence for *CAPB* linkage among prostate cancer families with a history of brain cancer (Gibbs et al., 1999b). In this original analysis of 141 families, in a genome scan of 94 families, and in the current analysis of 149 families, results of the dataset as a whole, regardless of the presence of brain cancer, are consistent with having a subset of families linked to *CAPB* (positive lod scores at high θ s) (Gibbs et

al., 1999b; Gibbs et al., 2000). Independent analysis of another collection of families (the ACTANE dataset) found suggestions of *CAPB* linkage among families with young mean age at diagnosis (Hlod = 1.17) regardless of brain cancer family history (Badzioch et al., personal communication). In the current analysis, positive lod scores and NPL scores were seen in a variety of age at diagnosis groups with no obvious trend. Some evidence for linkage to *CAPB* was observed among 37 white families with at least one man with poorly differentiated (high-grade) disease (NPL = 1.82, p = 0.04 at both *CAPB* markers). This result was strengthened (NPL = 2.44, p=0.01) by the removal of 20 families with potential linkage to other loci (lod > 0.1 at *HPC1*, *PCaP*, or *HPCX*). These results may indicate that linkage to *CAPB* may be more common in families with high-grade prostate cancers. This result is supported by a study that found evidence for linkage in the *CAPB* region ($p < 0.01$) when prostate cancer was considered as a quantitative trait using the Gleason score of tumor grade (Witte et al., 2000).

CAPB results when families were stratified by stage suggested that the most evidence for linkage was in 63 families with localized disease only, though results were non-significant (NPL= 1.15, p = 0.13 at D1S407). When families with evidence of linkage to another locus were excluded, multipoint Hlods became positive for the 39 families with local stage only and 22 families with local and regional stage. Grade and stage classifications were correlated in this dataset, though there are only 9 families with at least one high-grade case and at least one distantly-metastasized disease. Because families with high-grade disease had the most evidence for *CAPB* linkage, it is surprising that families with localized disease had the largest (still weak) suggestion of *CAPB* linkage.

CAPB linkage was originally observed in a subset of the currently analyzed prostate cancer families: 12 families with a history of brain cancer produced a lod score of 3.22 (θ =0.06, D1S507), and 6 of these families that had a mean age at prostate cancer diagnosis < 66 years produced a lod of 3.65 (θ =0.00, D1S407) (Gibbs et al., 1999b). In the current analysis, two of these families with brain cancer (one younger-onset, one older-onset) were included in the group of 17 families having at least one high-grade case and minimal evidence for linkage to other loci (Gibbs et al., 1999b). A comparison of these two families compared to the 15 families without history of brain cancer indicates that the suggestive *CAPB* results in this group of families with high-grade disease are not solely due to the two families with brain cancer. The ranges of results at marker D1S407 for the 15 families without brain cancer were as follows: 2-point lod scores, –0.25 to 0.31; multipoint lod scores, –0.28 to 0.36; and NPL scores, -0.82 to 1.73. The two families with brain cancer produced 2-point lod scores of 0.13 and 0.31, multipoint lod scores of 0.08 and 0.49, and NPL scores of 0.45 and 1.63. Results for these two families differ slightly from the original analysis, because, in the original analysis, brain cancer cases were coded as affected and prostate cancer cases not related to the brain cancer cases were coded as unknown affected status allowing a different genetic model with very low phenocopy rates to be used (Gibbs et al., 1999b).

Confirmation studies of *CAPB* have not observed particular evidence for linkage to *CAPB* among prostate cancer families with brain cancer. Badzioch et al. (personal communication) studied *CAPB* markers in 9 prostate cancer families with brain cancer and found positive lod and NPL scores (NPL = 0.51, p=0.29) among younger-onset families and negative lod score (NPL = -0.20, p=0.55) among older-onset families.

However, this effect of increasing evidence for linkage with younger mean age at diagnosis was also present among families without brain cancer, so the strongest indicator of potential linkage may be age at diagnosis and not brain cancer (Badzioch et al., personal communication). Berry et al. (2000) studied 13 prostate cancer families with brain cancer and 131 without brain cancer and did not find evidence for *CAPB* linkage in either group. These two studies did not code brain cancer cases as affected, as was done in the original analysis, so this may have affected the discrepancy.

It was originally hypothesized that *CAPB* had a high penetrance for prostate cancer, but a very low penetrance for brain cancer; of the original families selected for having brain cancer, 24 percent of affected cases had brain cancer and 76 percent had prostate cancer (Gibbs et al., 1999b). Thus, it is possible that family groups in the current analysis with potential evidence for *CAPB* linkage (possibly high-grade prostate cancer) include non-penetrant or unreported brain cancer. Epidemiologic studies showing familial aggregation of prostate and brain cancer (Goldgar et al., 1994) and studies of allelic loss in brain cancer tumors in the 1p36 region (Kraus et al., 1995) support the hypothesis of a genetic connection between these cancers. It is possible, however, that the original observation of evidence for *CAPB* linkage in prostate cancer families with brain cancer and lack of evidence for *CAPB* linkage in families without brain cancer (Gibbs et al., 1999b) resulted from a chance occurrence of brain cancer among *CAPB*-linked families.

The goal of the current analysis was to explore evidence for linkage to four previously reported loci in *a priori*-defined subgroups of prostate cancer families. This

was attempted in order to identify characteristics of families that may be linked to each of these loci. Additional families with similar clinical phenotypes can then be targeted for future linkage and positional cloning studies. Power to detect linkage was expected to be increased with stratification of families based on clinical characteristics, however it is important to consider the validity of this approach and the value of the stratifications we used. Though a price in power is paid with smaller sample sizes and the probability of type 1 error may be increased because of multiple comparisons, this approach may be useful as an exploratory analysis of clinical characteristics and evidence for linkage.

The power of linkage analysis is increased when families are genetically homogeneous (Ott, 1999). We have previously demonstrated the magnitude of this homogeneity effect in this collection of families (Jarvik et al., 1999). Computer simulations were conducted with the program SIMLINK using the pedigree structures and availability of DNA of the first 114 Caucasian families collected in our study. The power to detect lod scores over certain thresholds was calculated assuming an autosomsal dominant susceptibility locus and a varying proportion of families linked. Results for a marker with polymorphic information content of 0.7 are presented in Table 2-23 and Table 2-24 which are reprinted from Jarvik et al. (1999). These results demonstrate in this dataset that power to detect linkage is increased with an increase in percentage of families linked to each locus. For instance, in families with mean age at diagnosis > 65 years, an increase in the proportion of families linked to a locus from 60 percent to 70 percent results in almost halving of the number of families needed to achieve the same power; 116 families with 60 percent linked have probability of 0.643 at $\theta = 0.05$, and 58 families with 70 percent linked have probability of 0.510 at $\theta = 0.05$ (Table 2-24).

The percentage of families linked to each locus (and therefore power to detect linkage) depends on the frequency of linkage at each locus among high-risk prostate cancer families in general. Original estimates of the proportion of families linked (α) to each of the four loci studied here ranged from 15 to 50 percent (Smith et al., 1996; Berthon et al., 1998; Xu et al., 1998b; Gibbs et al., 1999b). However confirmation studies of these loci have indicated that the proportion of families linked may be less than the original estimates, due possibly to "regression to the mean" or differences in family collections studied. Families studied by various research groups may differ with respect to clinical characteristics and these clinical characteristics may be related to likelihood of linkage to each locus. Description and consideration of the clinical characteristics of affected men in families studied (as is done in the current analysis) may aid our understanding of differences in evidence of linkage in different populations.

The current analysis relied on clinical data from the medical records of 505 affected men in 149 high-risk prostate cancer families. The cancers of these men were heterogeneous with respect to possible detection method, grade and stage at diagnosis, and primary treatment. Two hundred and fifty-seven men were treated by radical prostatectomy, allowing for additional information about the cancer to be obtained from the surgery or from the surgical specimen. Pathologic analysis of the prostate itself can result in a different classification of histologic grade of the surgical specimen than the biopsy specimen in as much as 25-40 percent of cases (Garnett et al., 1984; D'Amico et al., 1999; Iczkowski et al., 1999). Of 174 men with known Gleason score at biopsy and known grade from prostatectomy specimen, 33 men (19 percent) were "upgraded" and 8 men (5 percent) were "downgraded". In the general population, up to 50-59 percent of

cases are upstaged at prostatectomy meaning that because of their surgery, the cancer was found to have spread to a larger extent than was suspected at initial clinical examination (Bostwick, 1997; Selley et al., 1997). Of 236 men in the current analysis with known clinical and pathologic stage, 74 men (31 percent) were "upstaged" from having localized disease at prostatectomy including 63 (27 percent) men found to have regional spread and 11 men (5 percent) found to have lymph node involvement or other metastases. The slightly lower rates of upgrading and upstaging in this study than in the population-based data may be due to increased screening among men in high-risk families. Nonetheless, in this data, the fact that some men were upgraded or upstaged while 248 men who did not have a prostatectomy don't have this pathologic data available could result in misclassification, particularly among the lower-grade or lower-staged families. One way that this could be addressed would be to consider only the clinical stage of affected men, as opposed to additionally considering the pathologic stage when available. However, we felt that utilizing the most reliable available data on affected men would be appropriate.

Medical records were available only for participating affected men; clinical data from deceased affected men were not included in stage and grade distributions or in age of diagnosis calculations. Thus a survival bias may be incurred by the use of prevalent cases in these families. Clinical factors associated with poor survival include young age at diagnosis, high-grade disease and advanced stage disease (Stanford et al., 1998; Ries et al., 2000). Additionally, men diagnosed prior to PSA screening (prior to the late 1980s) have lower 5-year survival rates than men diagnosed today (Stanford et al., 1998; Ries et al., 2000), perhaps because PSA-detected disease tends to be lower-grade and lower-stage or because of lead-time bias.

Men with medical records in these 149 families had a tumor grade distribution of 17 percent well-differentiated, 67 percent moderately differentiated, 9 percent poorly-differentiated, and 7 unknown. This may be skewed to lower grades when compared to data from the SEER program (1973-1995) which show a tumor grade distribution of approximately 24 percent well-differentiated, 41 percent moderately differentiated, 21 percent poorly differentiated, and 14 percent unknown (Stanford et al., 1998). In the current study of 149 families, 70 percent of cases had localized disease, 18 percent had regional spread, 6 percent had distant metastases, and 7 had unknown stage. SEER data 1989-1996 suggest that about 60 percent of cases are localized disease, 20 percent are regional, 8 percent had distant metastases, and 12 percent were unstaged (Ries et al., 2000). This may reflect survival bias because men in these high-risk families who had medical records available were living prevalent cases; i.e., men in these families who were deceased and had no records available may be cases with poorly-differentiated disease. This may also reflect that men in high-risk families are more thoroughly screened and therefore prostate cancers are diagnosed before tumors become poorly differentiated or metastasized.

One-hundred and fifty-seven affected men in 88 families did not have medical records available. Missing clinical data could have affected this analysis in several ways. Missing data can result in misclassification of families by age at diagnosis, grade, or stage groups, leading to bias towards the null when linkage results of strata are compared. Additionally, deceased affected men also did not have genotypes available and therefore linkage results for each family, depending on whether or not the man with missing data

shared the risk allele could be false positive or false negative. This is true also when unaffected men are not genotyped in parametric lod score analysis.

It is important to consider whether the amount of missing clinical data varied by family characteristics. Grouped median age at diagnosis (< 60, 60-64, 65-69, 70+ years) was not independent of whether a family included an affected men with missing clinical data ($\chi^2 = 9.29$, $p = 0.019$). Fewer older-onset families were missing medical record data (40 percent of families with median age $\geq$ 70 years and 55 percent of families with median age $\geq$ 65 years were missing at least some clinical data), compared to younger-onset families (73 percent of families with median age < 60 years, 66 percent of families with median age <65 years). This is not surprising, considering that men diagnosed at younger ages are less likely to survive. The amount missing medical record data did not appear to be related to grade groups, stage groups, maximum year of diagnosis, or median year of diagnosis (<1990, 1990-1995, 1995-1999).

Between 1985 and 1995, SEER data indicate that there was a steep increase in the incidence rate of localized stage disease (Stanford et al., 1998). This trend is apparent in the current data, because the stage groups used here (all localized, at least one regional, at least one distant) are not independent of the median year of diagnosis (1985-1989, 1990-1995, 1995-1999) (Fisher's exact $p = 0.004$). SEER data also indicate that there has been a substantial increase in moderately differentiated tumors during the PSA era (Stanford et al., 1998). No significant association between median year of diagnosis and stage group was seen here, however 32 percent of families with 1985-1989 median year at diagnosis had all moderate-grade disease, while 40 percent of families with median year at

diagnosis of 1995-1999 had all moderate-grade disease. Most recent year of diagnosis has been used previously to indicate whether a family may contain PSA detected disease (Xu et al., 2000).

One hundred and three men in 79 families had tumors with a Gleason score of 7 (at prostatectomy if available, otherwise from biopsy) that were coded as moderately differentiated grade. Because Gleason 7 often results from the presence of a Gleason 4 pattern, there is some debate about classifying it as poorly-differentiated rather than moderately-differentiated (Green et al., 1998; Stanford et al., 1998; Albertsen, 1998; Tefilli et al., 1999). If the men in the current analysis who had Gleason 7 tumors were coded as having poorly-differentiated disease, then the distributions of grade, as considered in this analysis, would change for 56 families. Eleven families (rather than only 1) would have all high-grade cases, 46 (rather than 20) would have moderate and high-grade cases, 38 (rather than 18) would have low, moderate, and high-grade cases, 24 (rather than 60) would have all moderate grade disease, and 27 (rather than 47) would have low and moderate disease. Grouping families for stratified analyses as was done here would result in 30 families (rather than 50), 24 (rather than 60) with only moderate disease, and 95 families (rather than 39) with at least one high-grade case. With the increased number of high-grade cases considered, additional analyses stratifying families with at least two high-grade cases could be performed (43 families rather than 6).

Alternative groupings and stratifications of families based on clinical characteristics could have been used in this analysis. It is difficult to characterize families which include affected men with a variety of tumor grades and cancer stages.

One alternative would have been to give values of 1, 2, and 3, to low, moderate, and high-grade tumors, respectively, and to use the mean grade value to rank families (this could have also been done for stage). However, a mean grade value of 2 would not differentiate between families with low, moderate, and high-grade tumors and families with only moderate grade tumors. Families instead were characterized by the distribution of grade and stage, simply by the presence or absence of each grade (low, moderate, and high) and stage (localized, regionally spread, and distantly-metastasized). For analysis by grade, white families with only low grade tumors (n=2) and with low and moderate grade tumors (n=47) were grouped, and families with low, moderate, and high-grade tumors (n=16), with moderate and high grade tumors (n=20), and with only high grade tumors (n=1) were joined. For analyses by stage, families with both localized and regionally spread disease (n=51) and with only regionally-spread disease (n=4) were grouped, and families with localized, regionally spread, and distantly metastasized disease (n=21), with regionally spread and distantly metastasized disease (n=2), and with only distantly metastasized disease (n=2) were grouped. Grouping families with at least one high-grade and at least one advanced-stage disease was meant to create homogeneous groups of families which may have the most aggressive disease. We hypothesized that genetic cases may be more aggressive and that the presence of lower-graded and lower-staged men in these families may be due to increased screening. It may be that joining groups in these ways did not increase homogeneity, particularly by stage, when families with localized and regionally spread disease (n=51) and families with only regionally-spread disease (n=4) were grouped. Additionally, joining groups in these ways did not take family size into account and did differentiate between families with only one or more

than one high-grade case or advanced-stage case (the number of families with more than one high-grade case and with more than one advanced-stage case was small).

Stage and grade are both associated with poor prognosis and are themselves correlated. The creation of a variable "aggressive disease" was meant to represent a prostate cancer that was either high-grade or had spread beyond the prostate (either regionally or with distantly metastases or both). Families were then classified by considering the percentage of men that had aggressive disease.

The effect of PSA screening on different collections of high-risk prostate cancer families has been difficult to address, and may be an explanation for differences in replications studies of putative loci. One way to address the effects of PSA screening on the rate of phenocopies, age at diagnosis, and severity of disease is too consider year of diagnosis. A recent presentation at the American Urological Association described that the likelihood of being linked to *HPC1* is greater in families where all the cases were diagnosed at earlier dates (before 1990 when PSA screening became routine) than later (before 1996) (Xu et al., 2000). In the current dataset of 149 families, only 3 families included men who were all diagnosed before 1990, and analysis of families at *HPC1* did not reveal stronger evidence in these families. Year of diagnosis, however, is a crude measure of whether a case is PSA-detected. The medical records of the 505 men analyzed here indicated that 56 men had PSA-detected disease (Stage T1cNxMx). This is very likely to be an underestimate because many men had both a high PSA and an abnormal DRE and the medical records did not clearly indicate which indicated the need

for prostate biopsy. One way to "adjust" for PSA-detected disease would be to code these 56 men as having unknown affected status.

We attempted to directly reduce known genetic heterogeneity by restricting some analyses to families with lod scores less than a certain threshold cut-off at other loci. Such methods, however, are prone to misclassification. There will be families that are linked that have lod scores less than the threshold and families that are unlinked that have lod scores greater than the threshold. Lod scores don't necessarily reflect which families are mutation carriers. This can be seen by considering lessons learned from analyses of breast cancer families that showed discrepancies between evidence for linkage and the presence of mutations. In one study, three out of ten families with lod scores < -1.0 at *BRCA1* were found to carry *BRCA1* mutations (Narod et al., 1995), while families in another study that had positive lod scores at *BRCA1* and *BRCA2* did not appear to carry mutations (Ford et al., 1998). Not until the cloning of any of the putative prostate cancer susceptibility loci will we accurately be able to assess and describe which families are linked to each locus.

We used a cut-off of lod ≥ 0.1 to indicate a family may have linkage to a locus. This was chosen because an analysis of heterogeneity estimated that 50 percent of our families were linked to these 4 loci and approximately 50 percent of our families were removed with this cut-off. If the lod cut-off of 0.1 were too high, some families would be included that may be linked to other loci; if the lod-cut off of 0.1 were too low, some families would be excluded that may not be linked to other loci. This approach is problematic additionally, because the expected lod score of each family if it were fully

linked vary by the size of the family and the number of affected men. Thus, an approach that considered a family's lod score at a locus as a fraction of the maximum expected lod score per family might better eliminate families with potential evidence for linkage. However, finding the transmission of mutations will be the most accurate way to eliminate families whose prostate cancer is due to a particular locus.

The problem of locus heterogeneity is indeed difficult. It is clear that multiple loci are involved in hereditary prostate cancer and it may be that several loci act together to increase risk. Methods of linkage analysis which incorporate the simultaneous consideration of linkage to two or more loci would greatly benefit the field of prostate cancer genetics.

Lod scores greater than 3.0 have traditionally been considered significant evidence for linkage for Mendelian diseases, while lod scores less than -2.0 are considered evidence against linkage (Morton, 1955; Ott, 1999). This is based on sequential testing of families with power=0.99 and a significance level of 0.001. Thus a lod score of 3.0 indicates that the probability of the data under the null hypothesis is about 0.001. Bayes theorem can be used to calculate the probability of the null (and alternative) hypotheses given the data (posterior probabilities); using a prior probability of linkage=0.02 and of no linkage=0.98, the posterior probability of no linkage given the data (posterior false-positive rate) = 0.047 (Morton, 1955). If this posterior false-positive rate increases with the number of markers tested, than adjustment for multiple markers needs to be done. It has been shown that when multiple markers are used, however, that the prior probability of linkage increases (for Mendelian traits), as does the significance

level and no correction is necessary (Risch, 1991). With complex traits however, it is unclear whether the prior probability of linkage increases with multiple markers being tested, so there is a debate in the genetics community about the best lod score threshold to use in genome-wide scans of complex diseases including continuing to use 3.0 (Morton, 1998), 3.3 (Lander et al., 1995), or 3 + $\log_{10}(g)$ where g is the number of markers tested (Kidd et al., 1984).

There is a similar problem with multiple testing in the current analysis; significant results may occur by chance, even when no linkage exists, because we have created multiple groups in which to assess linkage. The average numbers of family strata analyzed at each locus was 17.75, including 4 median age groups, 3 grade groups, 3 stage groups, 3 aggressive disease groups, 4 year of diagnosis groups (for *HPC1* only) and 3 mode of transmission group (for *HPCX* only). Because each analysis was repeated with exclusion of linkage to other loci (except one group which would result in no families) the number of analyses increased to approximately 35. A conservative approach to adjust for multiple comparisons would be the Bonferonni adjustment (Kidd et al., 1984). Thus, the required p-value for this stratified analysis would be 0.05/35 = 0.0014, and the required lod score (Z_c) for significant linkage would be

$$Z_c = Z + \log_{10}(35) = 3.00 + 1.54 = 4.54$$

Using this significance criteria, there were no significant results from this analysis. The most suggestive NPL score in this analysis was for 17 Caucasian families with at least one man with high-grade disease NPL=2.44 (p=0.011). However, this required lod score

is overly conservative because the approximate 35 strata are not independent (for example, stage and grade are correlated).

We did not make any adjustment for multiple comparisons to the p-values presented in the current analysis. Because of the controversy over significance levels in linkage analysis, it has been recommended to simply state the p-values and lod scores obtained without correcting for adjustments, so that they can be interpreted by the reader (Curtis, 1996; Witte et al., 1996). It is unclear how exactly to adjust p-values from multiple strata that are not independent as in this dataset. Further, the prior probability of linkage to the regions assessed is increased because this is a confirmation study. We have previously examined linkage to the four regions analyzed here in our entire unstratified dataset, and for most of the regions, results were consistent with the presence of a linked subset (positive lod scores at high values of θ). We therefore chose characteristics based on *a priori* hypothesis that may differentiate possibly-linked and possibly-unlinked families (we did not expect linkage in each subgroup). Nonetheless, the most elegant approach to determining the significance of any one result, would be to use computer simulation to find the empirical significance level (Lander et al., 1995; Ott, 1999). This was not done in this exploratory analysis, and any suggestive result presented here should be interpreted with caution. Similar analysis in independent datasets should be conducted.

If a clinical characteristic such as age at diagnosis or disease severity defines a linked subgroup of families, then more genetically homogeneous groups are created and power is increased when a dataset is stratified by this factor (Ott, 1999). However, such

stratification comes at a price (reduced sample size and the need to adjust for multiple comparisons) when it does not define a linked subset of families. Leal and Ott (2000) performed simulation study examining the costs and benefits of stratification in linkage analysis of affected-sib-pair (ASP) data. The ASP method assesses the identical-by-descent (IBD) allele sharing of affected sibs. ASPs were assigned a value of a variable *u* (such as onset age) that might be thought to have genetic effect, but did not in their simulation. ASPs were then stratified into 5 equally-sized classes of this variable *u* and a Bonferroni adjustment for multiple comparisons was made. A significance level of 0.05 was achieved when IBD allele-sharing probability was 0.57 without stratification, but with (useless) stratification, the gene had to show a much stronger effect (IBD sharing of 0.60) to produce the same significance (Leal and Ott, 2000). The need for a strong effect of stratification in order to be useful in linkage analysis is expected (Ott, 1999; Leal and Ott, 2000).

In summary, this analysis of four putative prostate cancer loci (*HPC1*, *PCaP*, *HPCX*, and *CAPB)* examined linkage in families with particular *a priori*-defined clinical characteristics. A few patterns or trends may have been apparent. Put in very general terms, our results indicate that *HPC1* may exist among families with older-onset disease and aggressive disease, *PCaP* may exist among densely-affected or younger-onset families, and *CAPB* linkage may exist among families with high-grade disease. These results must be interpreted with caution, because adjustment for multiple comparisons was not performed and because sample sizes were very small for some family groups. Nonetheless, this study may provide clues as to which type of families should be studied in independent analyses or pooled analyses to try to confirm, understand, or clone these

putative prostate cancer loci. Such an approach may be useful to the understanding of *HPC20* .

TABLE 2-1. LIABILITY FUNCTIONS USED

Liability Class*	Inclusion Criteria	Genotype-specific Penetrances**			Penetrance Ratio‡
		pp	Pp	PP†	
1	Affected men 30 - 49	0.000038	0.0018	0.0018	47.4
2	Affected men 50 - 59	0.00061	0.0084	0.0084	13.8
3	Affected men 60 - 69	0.0032	0.03	0.03	9.4
4	Affected men 70 - 79	0.0082	0.04	0.04	4.9
5	Affected men 80+	0.0086	0.015	0.015	1.7
6	Unaffected men 30 - 49	0.00019	0.0092	0.0092	48.4
7	Unaffected men 50 - 59	0.0032	0.06	0.06	18.7
8	Unaffected men 60 - 69	0.022	0.25	0.25	11.4
9	Unaffected men 70 - 79	0.079	0.61	0.61	7.7
10	Unaffected men 80+	0.16	0.88	0.88	5.5
11	Men <30, women	0.00	0.00	0.00	1.0

* For Xq27-28 analyses, an X-linked version of this model was used.

** Penetrances represent the probability that someone with the given genotype will be affected. For liability classes 1-5, this is the probability of becoming affected during the age group shown, and for liability classes 6-11, this is the probability of becoming affected before or during the age group shown.

† Allele P is the prostate cancer disease allele with frequency = 0.003.

‡ Penetrance ratio is penetrance of pP/PP genotype + penetrance of pp genotype.

TABLE 2-2. DESCRIPTIONS OF 505 AFFECTED MEN WITH CLINICAL DATA

	N (%)
Source of diagnosis confirmation	
Physician statement	502 (99%)
Operative report	237 (47%)
Path report from biopsy	331 (66%)
Path report from surgery	232 (46%)
Age at diagnosis*	
< 60 years	104 (20%)
60 - 64 years	112 (21%)
65 - 69 years	138 (26%)
70+ years	175 (33%)
Year of diagnosis	
1974-1979	7 (1%)
1980-1984	21 (4%)
1985-1989	67(13%)
1990-1994	293 (58%)
1995-1999	117 (24%)
Elevated PSA (> 4.0 ng/ml)	364 (72%)
PSA level at diagnosis	
< 4 ng/ml	26 (5%)
4 - < 10 ng/ml	167 (33%)
10-19.99 ng/ml	99 (20%)
20 + ng/ml	82 (16%)
Unknown	131 (26%)
Digital rectal exam result	
Abnormal	282 (56%)
Normal	100 (20%)
Unknown	123 (24%)
Gleason score† from biopsy	
2-4	71 (14%)
5-6	190 (37%)
7	65 (13%)
8-10	19 (4%)
Unknown	160 (32%)
Gleason score† from prostatectomy	
2-4	17 (4%)
5-6	100 (20%)
7	65 (13%)
8-10	25 (5%)
Unknown	51 (10%)
No prostatectomy	247 (49%)

TABLE 2-2 (CONTINUED). DESCRIPTIONS OF 505 AFFECTED MEN WITH CLINICAL DATA

	N (%)
Grade (from prostatectomy specimen, if available)	
Well-differentiated (low-grade)	88 (17%)
Moderately-differentiated (moderate-grade)	338 (67%)
Poorly-differentiated (high-grade)	45 (9%)
Unknown	34 (7%)
Clinical stage (from biopsy)	
Localized disease (Stage A or B)‡	427 (85%)
Regional spread (Stage C)	26 (5%)
Distant metastasis (Stage D)	18 (4%)
Unknown	34 (7%)
Pathologic stage (from prostatectomy)	
Localized disease (Stage A or B)	160 (32%)
Regional spread (Stage C)	64 (13%)
Distant metastasis (Stage D)	12 (2%)
No prostatectomy	224 (44%)
Unknown	44 (9%)
Summary Stage §	
Localized disease (Stage A or B)	353 (70%)
Regional spread (Stage C)	89 (18%)
Distant metastasis (Stage D)	29 (6%)
Unknown	34 (7%)
Aggressive Disease (high-grade or Stage C/D)	
Yes	139 (28%)
No	351 (69%)
Unknown	15 (3%)
Primary Treatment	
Radical Prostatectomy	257 (51%)
Radiation	140 (28%)
Orchiectomy	22 (4%)
Hormones alone	34 (7%)
Watchful waiting	20 (4%)
Other treatment	2 (0.04%)
Unknown	29 (6%)

* Age at diagnosis includes additional data from 24 men without medical records, but with written self-report of age at diagnosis.

† A Gleason score is a measure from 2-10 of the amount of loss of differentiation in a tumor.

‡ Twenty five men with unknown clinical stage who had surgery were assumed to have clinical Stage A or B.

§ Summary stage represents pathologic stage for 237 on whom it was available; otherwise clinical stage is used.

TABLE 2-3. CLINICAL DATA BY FAMILY

	Total (n=149)	White (n=143)
Median age at diagnosis per family*		
< 60 years	15 (10%)	13 (10%)
60 - 64 years	36 (24%)	34 (23%)
65 - 69 years	55 (37%)	54 (38%)
70+ years	43 (29%)	42 (29%)
Most recent year of diagnosis per family		
1983-1989	3 (2%)	3 (2%)
1990-1991	11 (7%)	11 (8%)
1992-1994	59 (40%)	57 (40%)
1995-1997	67 (45%)	64 (45%)
1998-1999	9 (6%)	8 (6%)
Grade distributions per family**		
All low grade	3 (2%)	2 (1%)
Low and moderate grade	47 (32%)	47 (33%)
All moderate grade	60 (40%)	57 (40%)
Low -> high-grade	18 (12%)	16 (11%)
Moderate and high-grade	20 (13%)	20 (14%)
All high-grade	1 (1%)	1 (1%)
Stage distribution per family†		
All localized disease	63 (42%)	63 (44%)
Localized and regional disease	55 (37%)	51 (36%)
All regional disease	5 (3%)	4 (3%)
Localized -> distant disease	22 (15%)	21 (15%)
Regional and distant disease	2 (1%)	2 (1%)
All distant metastasis	2 (1%)	2 (1%)
Amount of "aggressive disease" per family‡		
No cases	53 (36%)	53 (37%)
Less than 50 percent of cases	62 (42%)	59 (41%)
50 percent or more of cases	34 (23%)	31 (22%)
75 percent or more of cases§	10 (7%)	9 (6%)
All cases§	6 (4%)	5 (3%)

*Based on all sampled affected men

** Grade data is from prostatectomy specimen, if available.

† Stage represents pathologic stage for 237 on whom it was available; otherwise clinical stage was used.

‡"Aggressive disease" represents high-grade or Stage C or D disease

§ A subset of the preceding group

TABLE 2-4. LOD SCORES AT *HPC1*, ALL FAMILIES

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlo	θ	Hlod	θ	lod	α***	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
149 Fam	D1S1589	0.00	0.50	0.00	0.50	-10.87	0.01	-0.01	-0.696	0.754	80	0.123	0.28	0.123	0.28	-1.512	0.26	0.251	0.223	0.404
	D1S2883	0.01	0.42	0.01	0.42	-11.14	0.01	-0.01	-0.278	0.603		0.273	0.18	0.273	0.18	-0.950	0.32	0.323	0.982	0.163
	D1S2818	0.02	0.40	0.02	0.40	-11.83	0.03	-0.00	-0.034	0.507		0.394	0.16	0.394	0.16	-2.106	0.13	0.027	0.785	0.214
	D1S2127	0.13	0.32	0.13	0.32	-13.52	0.00	-0.01	-0.232	0.585		0.235	0.22	0.235	0.22	-3.343	0.00	-0.003	0.572	0.279
	D1S518	0.00	0.50	0.00	0.50	-14.50	0.00	-0.00	-0.175	0.563		0.003	0.40	0.004	0.34	-3.589	0.00	-0.003	0.924	0.176
	D1S1660	0.43	0.24	0.43	0.24	-9.32	0.00	-0.00	0.071	0.465		0.270	0.22	0.270	0.22	-2.897	0.01	-0.006	0.598	0.270

* Parametric analyses used Model b+

** Excludes families with lod scores < 0.1 at D1S2785, DXS984, and D1S407.

***Estimates of the proportion of families linked (α) without the inclusion of confidence contours should not be overinterpreted.

TABLE 2-5. LOD SCORES AT *HPC1*, WHITE FAMILIES STRATIFIED BY MEDIAN AGE AT DIAGNOSIS

											Excluding Families with Possible Linkage to Other Loci									
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
< 60 years	D1S1589	0.000	0.50	0.000	0.50	-1.746	0.001	-0.0008	-1.863	0.974	3	0.040	0.28	0.040	0.28	-0.187	0.0030	-0.0006	-1.176	0.875
(13 families)	D1S2883	0.000	0.50	0.000	0.50	-2.400	0.000	-0.0004	-2.084	0.986		0.055	0.22	0.055	0.22	-0.219	0.0021	-0.0005	-1.401	0.921
	D1S2818	0.000	0.50	0.000	0.50	-3.547	0.000	-0.0003	-2.643	0.998		0.557	0.00	0.557	0.00	-0.345	0.0008	-0.0003	-2.009	0.984
	D1S2127	0.000	0.50	0.000	0.50	-3.645	0.000	-0.0002	-2.697	0.998		0.025	0.22	0.025	0.22	-0.389	0.0006	-0.0003	-2.165	0.984
	D1S518	0.000	0.50	0.000	0.50	-1.841	0.000	-0.0006	-1.760	0.966		0.079	0.12	0.190	0.00	-0.404	0.0004	-0.0002	-2.339	0.984
	D1S1660	0.063	0.20	0.063	0.20	-3.831	0.000	-0.0003	-2.871	0.999		0.178	0.10	0.178	0.10	-0.318	0.0009	-0.0003	-1.904	0.984
60-64 years	D1S1589	0.000	0.50	0.000	0.50	-2.467	0.029	-0.0042	0.470	0.308	13	0.035	0.28	0.035	0.28	-1.542	0.0004	-0.0005	-0.593	0.713
(33 families)	D1S2883	0.000	0.50	0.000	0.50	-3.609	0.003	-0.0022	-0.374	0.634		0.000	0.50	0.000	0.50	-1.191	0.0006	-0.0005	-0.675	0.742
	D1S2818	0.118	0.20	0.118	0.20	-3.766	0.003	-0.0022	0.036	0.470		0.137	0.18	0.137	0.18	-1.149	0.0010	-0.0007	-0.456	0.662
	D1S2127	0.000	0.50	0.000	0.50	-3.952	0.002	-0.0018	-0.159	0.549		0.178	0.14	0.178	0.14	-1.096	0.0011	-0.0007	-0.371	0.629
	D1S518	0.018	0.34	0.018	0.34	-4.070	0.001	-0.0013	-0.484	0.675		0.000	0.50	0.000	0.50	-1.258	0.0011	-0.0008	-0.159	0.544
	D1S1660	0.047	0.28	0.060	0.00	-3.793	0.003	-0.0024	0.108	0.442		0.000	0.50	0.000	0.50	-1.045	0.0021	-0.0010	0.127	0.430
65-69 years	D1S1589	0.002	0.44	0.002	0.44	-5.051	0.000	-0.0011	-0.235	0.581	23	0.058	0.26	0.058	0.26	-0.396	0.3380	0.1249	0.739	0.224
(55 families)	D1S2883	0.014	0.38	0.014	0.38	-5.846	0.000	-0.0012	-0.801	0.785		0.530	0.08	0.530	0.08	-0.218	0.4009	0.2054	1.122	0.133
	D1S2818	0.002	0.42	0.002	0.42	-5.163	0.014	-0.0043	-0.103	0.528		0.356	0.12	0.356	0.12	-0.208	0.4309	0.1940	1.568	0.065
	D1S2127	0.142	0.28	0.170	0.00	-6.497	0.001	-0.0018	-0.287	0.601		0.337	0.14	0.337	0.14	-1.375	0.0094	-0.0029	1.114	0.134
	D1S518	0.000	0.50	0.000	0.50	-5.396	0.000	-0.0011	-0.713	0.757		0.000	0.50	0.000	0.50	-1.414	0.0375	-0.0042	1.025	0.153
	D1S1660	0.011	0.38	0.011	0.38	-7.299	0.000	-0.0007	-0.579	0.711		0.421	0.12	0.421	0.12	-0.510	0.3324	0.1192	1.150	0.127
70+ years	D1S1589	0.079	0.26	0.079	0.26	0.210	0.607	0.2629	0.733	0.228	38	0.035	0.26	0.035	0.26	0.138	0.5590	0.1996	0.409	0.333
(42 families)	D1S2883	0.171	0.18	0.171	0.18	0.471	0.698	0.5643	1.592	0.060		0.132	0.12	0.132	0.12	0.380	0.7642	0.3907	1.272	0.104
	D1S2818	0.665	0.00	0.665	0.00	0.724	0.844	0.7257	1.245	0.109		0.077	0.00	0.083	0.00	-0.251	0.3426	0.0319	0.751	0.223
	D1S2127	0.234	0.10	0.234	0.10	0.710	0.852	0.7103	1 288	0.101		0.000	0.50	0.000	0.50	-0.266	0.3198	0.0242	0.794	0.211
	D1S518	1.525	0.00	1.525	0.00	0.239	0.603	0.3495	0.702	0.237		1.009	0.00	1.009	0.00	0.187	0.6260	0.2146	1.310	0.098
	D1S1660	0.163	0.16	0.163	0.16	0.956	0.985	0.9512	1.593	0.060		0.000	0.50	0.000	0.50	-0.406	0.1330	-0.0092	0.435	0.324

* Parametric analyses used Model b+

** Excludes families with lod scores < 0.1 at D1S2785, DXS984, and D1S407.

TABLE 2-6. LOD SCORES AT *HPC1*, WHITE FAMILIES STRATIFIED BY DISTRIBUTION OF TUMOR GRADE

		2point*				Multipoint*					Excluding Families with Possible Linkage to Other Loci*** 2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
Low grade only	D1S1589	0.004	0.40	0.004	0.40	-2.003	0.011	-0.0046	-0.876	0.808	35	0.000	0.50	0.000	0.50	-1.324	0.0043	-0.0025	-1.095	0.864
or both low	D1S2883	0.011	0.36	0.012	0.00	-2.586	0.067	-0.0000	-0.323	0.618		0.029	0.24	0.030	0.16	-1.043	0.0204	-0.0053	-0.235	0.584
and moderate	D1S2818	0.000	0.50	0.000	0.50	-3.355	0.007	-0.0037	-1.048	0.853		0.144	0.08	0.166	0.00	-1.448	0.0029	-0.0021	-0.887	0.811
grade **	D1S2127	0.000	0.50	0.000	0.50	-3.461	0.006	-0.0035	-1.081	0.861		0.002	0.40	0.002	0.40	-1.518	0.0024	-0.0019	-0.932	0.823
(48 families)	D1S518	0.186	0.20	0.263	0.00	-2.411	0.042	-0.0051	-0.870	0.806		0.248	0.14	0.331	0.00	-1.324	0.0033	-0.0022	-0.604	0.721
	D1S1660	0.029	0.32	0.029	0.32	-3.175	0.004	-0.0030	-0.898	0.814		0.000	0.50	0.000	0.50	-1.754	0.0011	-0.0013	-1.068	0.858
All moderate	D1S1589	0.000	0.50	0.000	0.50	-3.180	0.047	-0.0026	0.559	0.282	26	0.297	0.14	0.297	0.14	0.012	0.5076	0.2851	1.176	0.122
grade	D1S2883	0.010	0.38	0.011	0.36	-4.250	0.016	-0.0048	-0.350	0.628		0.274	0.06	0.276	0.02	0.023	0.4985	0.2578	0.977	0.163
(58 families)	D1S2818	0.000	0.50	0.000	0.50	-6.127	0.000	-0.0010	-0.208	0.572		0.045	0.28	0.045	0.28	-1.228	0.0061	-0.0026	0.815	0.203
	D1S2127	0.171	0.26	0.171	0.26	-6.893	0.000	-0.0008	-0.292	0.605		0.429	0.10	0.429	0.10	-1.607	0.0017	-0.0014	0.858	0.192
	D1S518	0.000	0.50	0.000	0.50	-4.048	0.005	-0.0035	-0.254	0.591		0.000	0.50	0.000	0.50	-1.515	0.0130	-0.0036	1.237	0.111
	D1S1660	0.319	0.18	0.338	0.00	-6.867	0.000	-0.0010	-0.096	0.528		0.158	0.16	0.158	0.16	-0.494	0.2868	0.0589	1.422	0.082
At least 1 high-	D1S1589	0.000	0.50	0.000	0.50	-3.870	0.000	-0.0010	0.157	0.422	16	0.040	0.28	0.040	0.28	-0.553	0.1207	-0.0013	0.619	0.255
grade	D1S2883	0.001	0.46	0.001	0.46	-4.547	0.000	-0.0007	-0.059	0.508		0.055	0.22	0.055	0.22	-0.147	0.4054	0.0534	1.212	0.116
(37 families)	D1S2818	0.491	0.10	0.491	0.10	-2.270	0.237	0.2085	1.136	0.129		0.557	0.00	0.557	0.00	0.734	0.9829	0.7311	2.026	0.029
	D1S2127	0.086	0.30	0.184	0.00	-3.027	0.142	0.0838	0.880	0.186		0.025	0.22	0.025	0.22	0.010	0.5014	0.1361	1.565	0.066
	D1S518	0.001	0.46	0.001	0.46	-4.608	0.000	-0.0007	-0.303	0.605		0.079	0.12	0.190	0.00	-0.037	0.5030	0.1471	1.394	0.087
	D1S1660	0.019	0.40	0.019	0.40	-3.926	0.002	-0.0020	0.552	0.281		0.178	0.10	0.178	0.10	-0.130	0.4719	0.1247	1.019	0.153

* Parametric analyses used Model b+

** Represents grade from prostatectomy specimen, when available, otherwise, grade from biopsy specimen.

*** Excludes families with lod scores < 0.1 at D1S2785, DXS984, and D1S407.

TABLE 2-7. LOD SCORES AT *HPC1*, WHITE FAMILIES STRATIFIED BY DISTRIBUTION OF CANCER STAGE

												Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*						2point*				Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
Local only***	D1S1589	0.000	0.50	0.000	0.50	-4.235	0.000	-0.0016	-0.474	0.676	40	0.009	0.36	0.009	0.36	-1.993	0.0013	-0.0014	-0.9313	0.823
(63 families)	D1S2883	0.024	0.38	0.024	0.38	-5.404	0.001	-0.0016	-0.673	0.745		0.000	0.50	0.000	0.50	-2.011	0.0015	-0.0016	-0.3290	0.620
	D1S2818	0.146	0.26	0.146	0.26	-5.445	0.001	-0.0021	-0.910	0.817		0.276	0.16	0.276	0.16	-1.739	0.0062	-0.0032	-0.4392	0.662
	D1S2127	0.035	0.36	0.035	0.36	-6.473	0.000	-0.0010	-1.242	0.895		0.061	0.28	0.061	0.28	-2.661	0.0005	-0.0009	-0.8615	0.803
	D1S518	0.000	0.50	0.000	0.50	-5.539	0.000	-0.0011	-1.246	0.896		0.010	0.34	0.010	0.34	-2.562	0.0006	-0.0010	-0.4365	0.661
	D1S1660	0.110	0.28	0.110	0.28	-6.460	0.000	-0.0010	-0.946	0.827		0.000	0.50	0.000	0.50	-2.827	0.0004	-0.0008	-0.5981	0.719
Local/Regional	D1S1589	0.006	0.36	0.006	0.30	-1.394	0.268	0.1669	0.229	0.399	25	0.000	0.50	0.000	0.50	0.154	0.5626	0.2810	0.108	0.442
(55 families)	D1S2883	0.000	0.50	0.000	0.50	-2.458	0.111	0.0300	-0.407	0.649		0.858	0.00	0.858	0.00	0.659	0.9022	0.6544	0.389	0.337
	D1S2818	0.349	0.14	0.349	0.14	-2.675	0.108	0.0158	0.284	0.378		0.307	0.02	0.307	0.02	0.209	0.6525	0.2483	0.384	0.338
	D1S2127	0.137	0.20	0.143	0.00	-3.444	0.038	-0.0052	0.228	0.399		0.351	0.00	0.351	0.00	-0.128	0.4737	0.0821	0.490	0.301
	D1S518	0.195	0.24	0.317	0.00	-2.530	0.056	-0.0020	-0.513	0.689		0.864	0.00	0.864	0.00	0.503	0.7900	0.5239	0.994	0.159
	D1S1660	0.825	0.08	0.826	0.08	-2.893	0.160	0.0683	0.521	0.293		1.011	0.00	1.011	0.00	1.038	0.9907	1.0351	0.472	0.308
At least 1 distant	D1S1589	0.000	0.50	0.001	0.36	-3.423	0.000	-0.0006	0.221	0.394	12	0.224	0.16	0.224	0.16	-0.149	0.4885	0.1218	2.094	0.026
(25 families)	D1S2883	0.000	0.46	0.000	0.46	-3.522	0.000	-0.0009	0.619	0.257		0.420	0.04	0.420	0.04	0.103	0.5713	0.1652	2.474	0.013
	D1S2818	0.000	0.50	0.000	0.50	-3.632	0.036	0.0010	0.623	0.256		0.007	0.32	0.007	0.32	-0.424	0.1804	0.0079	2.284	0.018
	D1S2127	0.030	0.34	0.113	0.00	-3.465	0.065	0.0168	0.748	0.220		0.099	0.20	0.099	0.20	-0.337	0.2614	0.0240	2.346	0.016
	D1S518	0.000	0.50	0.000	0.50	-2.998	0.002	-0.0017	0.768	0.214		0.000	0.50	0.000	0.50	-0.830	0.0076	-0.0019	1.773	0.046
	D1S1660	0.000	0.50	0.000	0.50	-4.615	0.000	-0.0004	-0.001	0.481		0.000	0.44	0.000	0.44	-0.492	0.1087	-0.0020	1.938	0.035

* Parametric analyses used Model b+

** Excludes families with lod scores < 0.1 at D1S2785, DXS984, and D1S407.

*** Represents pathologic stage, when available, otherwise, clinical stage.

TABLE 2-8. LOD SCORES AT *HPC1* WHITE FAMILIES STRATIFIED BY AGGRESSIVE DISEASE

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*					Multipoint*			
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
None	D1S1589	0.000	0.50	0.000	0.50	-2.494	0.002	-0.0025	-0.171	0.559	35	0.035	0.28	0.040	0.00	-1.261	0.0055	-0.0029	-0.855	0.801
(52 families)	D1S2883	0.065	0.28	0.065	0.28	-3.631	0.005	-0.0034	-0.505	0.687		0.000	0.50	0.000	0.50	-1.345	0.0053	-0.0028	-0.285	0.603
	D1S2818	0.000	0.50	0.000	0.50	-5.512	0.000	-0.0009	-1.304	0.907		0.084	0.24	0.084	0.24	-2.013	0.0010	-0.0012	-0.798	0.784
	D1S2127	0.000	0.50	0.000	0.46	-5.682	0.000	-0.0008	-1.310	0.908		0.119	0.22	0.119	0.22	-2.124	0.0008	-0.0010	-0.842	0.797
	D1S518	0.000	0.50	0.000	0.50	-3.411	0.002	-0.0025	-0.941	0.826		0.075	0.24	0.075	0.24	-1.785	0.0011	-0.0013	-0.411	0.651
	D1S1660	0.165	0.22	0.165	0.22	-5.200	0.000	-0.0008	-0.953	0.829		0.000	0.50	0.000	0.50	-1.892	0.0008	-0.0011	-0.364	0.633
< 50%	D1S1589	0.003	0.44	0.003	0.44	-3.563	0.025	-0.0057	0.298	0.372	27	0.057	0.28	0.057	0.28	-0.944	0.2077	0.0440	0.973	0.164
(59 families)	D1S2883	0.004	0.46	0.004	0.46	-4.390	0.006	-0.0038	-0.109	0.532		0.470	0.10	0.470	0.10	-0.086	0.4676	0.2514	1.341	0.094
	D1S2818	0.298	0.22	0.298	0.22	-2.033	0.266	0.3157	1.097	0.136		0.742	0.00	0.742	0.00	0.254	0.5937	0.4015	1.744	0.047
	D1S2127	0.461	0.18	0.501	0.00	-3.739	0.112	0.0630	0.662	0.248		0.033	0.28	0.033	0.28	-1.127	0.0378	-0.0054	1.280	0.104
	D1S518	0.000	0.50	0.000	0.50	-5.023	0.001	-0.0017	-0.279	0.599		0.000	0.50	0.000	0.50	-1.800	0.0031	-0.0019	1.041	0.149
	D1S1660	0.203	0.24	0.203	0.24	-5.604	0.001	-0.0016	0.071	0.459		0.218	0.18	0.218	0.18	-0.722	0.2723	0.0697	1.108	0.135
>= 50%	D1S1589	0.000	0.50	0.000	0.50	-2.634	0.00	-0.003	-0.155	0.547	15	0.008	0.26	0.010	0.10	0.341	0.95	0.336	0.517	0.291
(31 families)	D1S2883	0.000	0.50	0.000	0.50	-3.362	0.00	-0.001	-0.133	0.538		0.330	0.00	0.330	0.00	0.264	0.89	0.258	0.815	0.202
	D1S2818	0.000	0.50	0.000	0.50	-4.207	0.00	-0.001	-0.168	0.553		0.000	0.50	0.000	0.50	-0.184	0.31	0.017	0.690	0.237
	D1S2127	0.000	0.50	0.000	0.50	-3.961	0.00	-0.001	0.005	0.483		0.278	0.00	0.278	0.00	0.135	0.65	0.151	0.891	0.183
	D1S518	0.002	0.42	0.003	0.00	-3.164	0.08	0.010	0.491	0.302		0.724	0.00	0.724	0.00	0.707	0.99	0.705	1.377	0.089
	D1S1660	0.000	0.50	0.000	0.50	-2.996	0.00	-0.001	-0.358	0.627		0.037	0.18	0.079	0.00	0.234	0.75	0.238	0.363	0.343
All†	D1S1589	0.000	0.50	0.000	0.50	-0.471	0.002	-0.0007	0.167	0.420	2	0.000	0.50	0.000	0.50	-0.010	0.49	-0.004	0.105	0.484
(5 families)	D1S2883	0.000	0.50	0.000	0.50	-0.810	0.000	-0.0003	-0.409	0.642		0.041	0.00	0.041	0.00	0.014	0.50	0.009	0.891	0.140
	D1S2818	0.043	0.00	0.043	0.00	-0.494	0.001	-0.0005	0.111	0.440		0.028	0.00	0.028	0.00	0.001	0.50	0.004	0.919	0.140
	D1S2127	0.011	0.20	0.013	0.00	-0.454	0.002	-0.0007	0.168	0.420		0.032	0.00	0.032	0.00	-0.001	0.49	0.002	0.894	0.140
	D1S518	0.000	0.50	0.000	0.50	-0.646	0.000	-0.0003	-0.789	0.767		0.000	0.50	0.000	0.50	-0.021	0.40	-0.004	0.718	0.156
	D1S1660	0.000	0.50	0.000	0.50	-0.427	0.002	-0.0007	0.158	0.430		0.032	0.00	0.032	0.00	-0.005	0.49	0.000	0.817	0.140

* Affected men were considered to have "aggressive disease" if they had high-grade (grade III) or Stage C or D cancer.
† The 5 families with all cases of aggressive disease are included in the group of families with 50 percent or more.
** Excludes families with lod scores < 0.1 at D1S2785, DXS984, and D1S407.

TABLE 2-9. LOD SCORES AT *HPC1* WHITE FAMILIES STRATIFIED BY MOST RECENT YEAR OF DIAGNOSIS

		2point*				Multipoint*					Excluding Families with Possible Linkage to Other Loci** 2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
1983-1989	D1S1589	0.000	0.50	0.000	0.50	-0.102	0.012	-0.001	-0.468	0.609	0									
3 families	D1S2883	0.000	0.50	0.000	0.50	-0.126	0.007	-0.001	-0.506	0.615										
	D1S2818	0.000	0.50	0.000	0.50	-0.287	0.001	-0.000	-0.689	0.734										
	D1S2127	0.000	0.50	0.000	0.50	-0.287	0.001	-0.000	-0.689	0.734										
	D1S518	0.000	0.50	0.000	0.50	-0.253	0.001	-0.000	-0.828	0.839										
	D1S1660	0.000	0.50	0.000	0.50	-0.184	0.003	-0.000	-0.699	0.734										
1990-1993	D1S1589	0.000	0.50	0.000	0.50	-5.577	0.000	-0.000	-1.308	0.908	25	0.019	0.36	0.019	0.36	-0.387	0.119	-0.005	-0.443	0.661
43 families	D1S2883	0.013	0.42	0.013	0.42	-5.748	0.000	-0.000	-0.486	0.678		0.044	0.30	0.044	0.30	-0.146	0.419	0.057	0.666	0.248
	D1S2818	0.003	0.46	0.003	0.46	-4.616	0.019	-0.003	-0.228	0.579		0.000	0.40	0.001	0.32	-0.385	0.207	0.005	0.300	0.372
	D1S2127	0.406	0.18	0.602	0.00	-4.246	0.059	0.010	-0.022	0.497		0.381	0.08	0.388	0.02	0.015	0.500	0.107	0.406	0.334
	D1S518	0.002	0.44	0.002	0.44	-4.724	0.001	-0.001	-0.213	0.573		0.090	0.28	0.150	0.00	0.505	0.871	0.500	0.880	0.188
	D1S1660	0.113	0.24	0.113	0.24	-2.585	0.007	-0.003	0.199	0.410		0.496	0.14	0.496	0.14	0.298	0.760	0.302	0.698	0.238
1994-1995	D1S1589	0.000	0.50	0.000	0.50	-4.201	0.017	-0.006	-0.403	0.650	41	0.141	0.18	0.159	0.00	-0.050	0.498	0.286	0.150	0.431
73 families	D1S2883	0.000	0.50	0.000	0.50	-5.009	0.009	-0.005	-0.707	0.757		0.041	0.20	0.120	0.00	-0.128	0.462	0.291	0.158	0.428
	D1S2818	0.078	0.30	0.078	0.30	-6.479	0.000	-0.001	-0.565	0.709		0.793	0.06	0.793	0.06	-0.713	0.269	0.082	0.231	0.400
	D1S2127	0.000	0.50	0.000	0.50	-8.540	0.000	-0.000	-1.055	0.855		0.000	0.50	0.000	0.50	-2.296	0.002	-0.001	-0.177	0.561
	D1S518	0.000	0.50	0.000	0.50	-8.757	0.000	-0.000	-0.985	0.837		0.000	0.50	0.000	0.50	-2.491	0.001	-0.001	-0.174	0.560
	D1S1660	0.000	0.50	0.000	0.50	-6.260	0.000	-0.001	-0.872	0.807		0.000	0.50	0.000	0.50	-2.305	0.001	-0.001	-0.374	0.638
1996-1999	D1S1589	0.019	0.36	0.019	0.36	-1.187	0.208	0.064	0.608	0.256	11	0.006	0.38	0.006	0.38	-1.426	0.000	-0.000	0.981	0.158
24 families	D1S2883	0.044	0.30	0.044	0.30	-0.499	0.367	0.228	0.989	0.157		0.156	0.14	0.156	0.14	-0.891	0.001	-0.000	1.235	0.113
	D1S2818	0.000	0.40	0.001	0.32	-0.369	0.402	0.265	1.126	0.130		0.000	0.50	0.000	0.50	-0.844	0.001	-0.000	1.215	0.116
	D1S2127	0.381	0.08	0.388	0.02	-0.310	0.422	0.290	1.213	0.115		0.312	0.06	0.319	0.00	-0.835	0.001	-0.000	1.275	0.107
	D1S518	0.090	0.28	0.150	0.00	-0.233	0.457	0.372	1.550	0.068		0.000	0.50	0.000	0.50	-0.892	0.001	-0.000	1.515	0.076
	D1S1660	0.496	0.14	0.496	0.14	-0.022	0.498	0.408	1.306	0.100		0.192	0.18	0.192	0.18	-0.373	0.192	0.009	1.180	0.121

* Parametric analyses used Model b+.
** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

TABLE 2-10. LOD SCORES AT *PCAP*, ALL FAMILIES

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*				Multipoint*				
Fams.	Marker	Maxlo	θ	Hlod	θ	lod	α	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
149 Fam	D1S235	0.00	0.50	0.00	0.50	-12.31	0.10	-0.00	-1.297	0.905	79	0.000	0.50	0.000	0.50	-3.883	0.00	-0.004	-0.663	0.743
	D1S2785	0.57	0.26	0.57	0.26	-9.34	0.10	0.22	-0.368	0.638		0.056	0.32	0.056	0.32	-3.442	0.01	-0.005	-0.157	0.554
	D1S547	0.33	0.28	0.33	0.28	-9.68	0.09	0.20	-0.354	0.633		0.572	0.14	0.572	0.14	-3.483	0.01	-0.005	-0.126	0.542
	D1S1609	0.11	0.32	0.11	0.32	-6.34	0.17	0.50	-0.050	0.513		0.000	0.50	0.067	0.00	-2.447	0.15	0.107	-0.046	0.510

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

TABLE 2-11. LOD SCORES AT *PCAP* WHITE FAMILIES STRATIFIED BY MEDIAN AGE AT DIAGNOSIS

											Excluding Families with Possible Linkage to Other Loci**									
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
< 60 years	D1S235	0.000	0.50	0.000	0.50	-2.423	0.000	-0.000	-1.155	0.877	7	0.000	0.50	0.000	0.50	-0.501	0.004	-0.001	-0.212	0.571
(13 families)	D1S2785	0.902	0.00	0.902	0.00	-0.372	0.271	0.035	0.239	0.395		0.925	0.00	0.925	0.00	0.382	0.992	0.381	1.163	0.126
	D1S547	0.112	0.22	0.112	0.22	-0.745	0.157	0.008	0.227	0.399		0.664	0.00	0.664	0.00	0.446	0.996	0.445	1.233	0.112
	D1S1609	0.479	0.10	0.479	0.10	0.422	0.860	0.428	0.793	0.211		0.594	0.00	0.594	0.00	0.562	0.998	0.561	1.255	0.109
60-64 years	D1S235	0.000	0.50	0.000	0.50	-3.837	0.001	-0.001	-0.589	0.714	11	0.000	0.46	0.101	0.00	0.496	0.818	0.505	0.732	0.220
(33 families)	D1S2785	0.030	0.34	0.031	0.30	-4.196	0.000	-0.001	-0.565	0.705		0.000	0.50	0.000	0.50	-0.800	0.002	-0.001	0.330	0.349
	D1S547	0.330	0.22	0.330	0.22	-3.811	0.000	-0.001	-0.464	0.668		0.405	0.06	0.405	0.06	-0.778	0.002	-0.001	0.386	0.329
	D1S1609	0.017	0.34	0.045	0.00	-1.772	0.063	-0.001	-0.242	0.582		0.096	0.08	0.164	0.00	0.163	0.605	0.216	0.458	0.304
65-69 years	D1S235	0.000	0.50	0.000	0.50	-5.367	0.001	-0.001	-1.110	0.869	28	0.000	0.50	0.000	0.50	-2.682	0.000	-0.000	-0.789	0.780
(55 families)	D1S2785	0.278	0.28	0.352	0.00	-4.539	0.134	0.242	-0.308	0.609		0.210	0.22	0.210	0.22	-1.780	0.011	-0.003	-0.462	0.666
	D1S547	0.004	0.40	0.009	0.08	-4.795	0.131	0.233	-0.319	0.614		0.000	0.50	0.000	0.50	-1.827	0.018	-0.004	-0.413	0.647
	D1S1609	0.000	0.50	0.099	0.00	-4.140	0.167	0.371	-0.345	0.624		0.000	0.50	0.012	0.00	-1.360	0.182	0.105	-0.498	0.679
70+ years	D1S235	0.028	0.26	0.028	0.26	-1.246	0.003	-0.002	-0.121	0.538	30	0.000	0.50	0.000	0.50	-0.895	0.002	-0.001	-0.635	0.731
(42 families)	D1S2785	0.000	0.50	0.000	0.50	-1.032	0.003	-0.002	-0.255	0.591		0.000	0.50	0.000	0.50	-0.907	0.002	-0.001	-0.584	0.714
	D1S547	0.000	0.50	0.000	0.50	-1.015	0.003	-0.002	-0.273	0.598		0.000	0.50	0.000	0.50	-0.915	0.002	-0.001	-0.625	0.728
	D1S1609	0.352	0.06	0.352	0.06	-0.756	0.006	-0.003	-0.082	0.522		0.000	0.50	0.000	0.50	-0.844	0.002	-0.001	-0.427	0.657

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

TABLE 2-12. LOD SCORES AT *PCAP* WHITE FAMILIES STRATIFIED BY TUMOR GRADE

		2point*				Multipoint*					Excluding Families with Possible Linkage to Other Loci***									
											2point*					Multipoint*				
Fams.**	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
All low grade	D1S235	0.115	0.20	0.115	0.20	-2.444	0.001	-0.001	-0.051	0.510	28	0.000	0.46	0.000	0.46	-0.885	0.004	-0.002	-0.050	0.509
or low and	D1S2785	0.026	0.32	0.035	0.00	-4.655	0.000	-0.000	-0.951	0.829		0.000	0.50	0.000	0.50	-1.210	0.011	-0.003	-0.245	0.586
Moderate	D1S547	0.000	0.46	0.000	0.46	-5.008	0.000	-0.000	-1.007	0.843		0.000	0.50	0.000	0.50	-1.184	0.009	-0.003	-0.342	0.624
Grade (n=48)	D1S1609	0.000	0.44	0.000	0.44	-4.171	0.000	-0.000	-1.089	0.863		0.000	0.50	0.000	0.50	-1.198	0.004	-0.002	-0.686	0.748
Moderate	D1S235	0.000	0.50	0.000	0.50	-5.145	0.012	-0.004	-0.985	0.837	32	0.000	0.50	0.000	0.50	-2.130	0.037	-0.002	-0.382	0.637
grade only	D1S2785	0.142	0.28	0.148	0.14	-2.902	0.163	0.165	0.068	0.462		0.032	0.30	0.032	0.30	-1.750	0.006	-0.003	0.374	0.343
(58 families)	D1S547	0.272	0.22	0.272	0.22	-3.039	0.149	0.139	0.051	0.468		0.498	0.12	0.498	0.12	-1.896	0.003	-0.002	0.344	0.353
	D1S1609	0.295	0.20	0.387	0.00	-0.594	0.401	0.795	0.778	0.215		0.332	0.14	0.418	0.00	-0.091	0.475	0.498	1.033	0.151
At least 1	D1S235	0.000	0.50	0.000	0.50	-5.284	0.000	-0.000	-1.439	0.932	16	0.000	0.50	0.000	0.50	-1.230	0.000	-0.000	-0.949	0.827
high-grade	D1S2785	0.316	0.24	0.323	0.16	-2.583	0.097	0.089	-0.034	0.498		0.120	0.16	0.120	0.16	-0.806	0.003	-0.001	-0.669	0.739
(37 families)	D1S547	0.039	0.32	0.052	0.16	-2.320	0.124	0.125	0.106	0.442		0.000	0.50	0.015	0.00	-0.625	0.055	-0.004	-0.395	0.638
	D1S1609	0.122	0.26	0.197	0.00	-1.480	0.181	0.179	0.020	0.476		0.000	0.50	0.000	0.50	-0.699	0.004	-0.001	-0.669	0.739

* Parametric analyses used Model b+.

** Represents grade of prostatectomy specimen, when available, otherwise, grade from biopsy specimen.

*** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

TABLE 2-13. LOD SCORES AT *PCAP* WHITE FAMILIES STRATIFIED BY CANCER STAGE

											Excluding Families with Possible Linkage to Other Loci**									
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
All local stage	D1S235	0.000	0.50	0.000	0.50	-5.800	0.000	-0.001	-0.899	0.814	37	0.000	0.50	0.000	0.50	-1.322	0.001	0.001	-0.322	0.617
(63 families)	D1S2785	0.000	0.50	0.000	0.50	-6.277	0.001	-0.001	-1.013	0.844		0.000	0.50	0.000	0.50	-1.834	0.001	-0.001	-0.436	0.661
	D1S547	0.000	0.50	0.000	0.50	-6.330	0.001	-0.002	-0.914	0.818		0.109	0.12	0.113	0.02	-1.642	0.001	-0.001	-0.328	0.619
	D1S1609	0.000	0.50	0.047	0.00	-3.722	0.037	0.001	-0.451	0.667		0.000	0.50	0.000	0.50	-1.509	0.001	-0.001	-0.319	0.616
Local &	D1S235	0.000	0.50	0.000	0.50	-5.283	0.000	-0.000	-0.969	0.833	26	0.000	0.50	0.000	0.50	-2.054	0.000	-0.000	-0.341	0.621
regional ***	D1S2785	0.944	0.12	0.944	0.12	-2.535	0.008	-0.004	-0.213	0.574		1.652	0.00	1.652	0.00	0.324	0.665	0.383	0.917	0.178
(55 families)	D1S547	0.313	0.20	0.313	0.20	-2.801	0.003	-0.002	-0.448	0.665		0.373	0.12	0.373	0.12	-0.064	0.488	0.169	0.498	0.300
	D1S1609	0.062	0.30	0.062	0.28	-2.520	0.122	0.059	-0.197	0.567		0.332	0.12	0.342	0.00	0.460	0.605	0.638	0.680	0.242
At least 1	D1S235	0.076	0.26	0.111	0.00	-1.790	0.137	0.042	-0.446	0.658	13	0.344	0.02	0.356	0.00	-0.207	0.358	0.147	-0.615	0.719
distant stage	D1S2785	0.320	0.24	0.346	0.00	-1.327	0.252	0.396	0.654	0.246		0.000	0.50	0.000	0.50	-1.596	0.000	-0.000	-0.993	0.840
(25 families)	D1S547	0.270	0.24	0.270	0.24	-1.237	0.277	0.453	0.914	0.177		0.000	0.50	0.000	0.50	-1.367	0.002	-0.001	-0.471	0.666
	D1S1609	0.513	0.14	0.513	0.14	-0.004	0.443	0.632	0.685	0.237		0.138	0.12	0.226	0.00	-0.429	0.255	0.043	-0.486	0.672

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

*** Represents pathologic stage, when available, otherwise, clinical stage.

TABLE 2-14. LOD SCORES AT *PCAP* WHITE FAMILIES STRATIFIED BY AGGRESSIVE DISEASE

		2point*				Multipoint*					Excluding Families with Possible Linkage to Other Loci** 2point*					Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
None	D1S235	0.000	0.50	0.000	0.50	-4.119	0.002	-0.002	-0.682	0.748	32	0.000	0.50	0.000	0.50	-1.727	0.001	-0.001	-0.366	0.633
(53 fams)	D1S2785	0.000	0.50	0.000	0.50	-4.961	0.007	-0.003	-1.005	0.842		0.000	0.50	0.000	0.50	-2.147	0.000	-0.000	-0.608	0.722
	D1S547	0.006	0.40	0.006	0.40	-5.070	0.008	-0.003	-0.883	0.810		0.283	0.00	0.283	0.00	-1.926	0.000	-0.001	-0.457	0.667
	D1S1609	0.036	0.30	0.129	0.00	-2.826	0.080	0.027	-0.488	0.681		0.000	0.50	0.000	0.50	-1.629	0.001	-0.001	-0.407	0.649
< 50%	D1S235	0.010	0.38	0.010	0.36	-4.508	0.002	-0.002	-0.699	0.753	31	0.078	0.22	0.079	0.18	-1.471	0.080	0.008	-0.323	0.613
(59 fams)	D1S2785	0.841	0.18	0.841	0.18	-3.239	0.128	0.156	0.385	0.340		0.381	0.16	0.381	0.16	-1.159	0.121	0.010	0.377	0.340
	D1S547	0.202	0.24	0.206	0.22	-3.360	0.127	0.153	0.366	0.347		0.099	0.22	0.099	0.22	-1.375	0.098	0.005	0.301	0.368
	D1S1609	0.237	0.26	0.266	0.00	-2.042	0.249	0.490	0.478	0.307		0.281	0.14	0.359	0.00	-0.105	0.451	0.495	0.345	0.352
>= 50%	D1S235	0.000	0.50	0.000	0.50	-4.246	0.00	-0.000	-1.117	0.870	13	0.000	0.50	0.000	0.50	-1.048	0.00	-0.000	-0.652	0.734
(31 fams)	D1S2785	0.004	0.34	0.058	0.00	-1.939	0.03	-0.002	-0.359	0.628		0.113	0.16	0.113	0.16	-0.460	0.02	-0.003	-0.144	0.543
	D1S547	0.042	0.32	0.042	0.32	-1.937	0.03	-0.002	-0.429	0.655		0.010	0.28	0.022	0.00	-0.403	0.05	-0.004	-0.148	0.544
	D1S1609	0.029	0.30	0.029	0.30	-1.378	0.02	-0.005	-0.313	0.610		0.001	0.38	0.025	0.00	-0.254	0.23	0.000	-0.022	0.495
All†	D1S235	0.000	0.50	0.000	0.50	-0.541	0.000	-0.000	-1.165	0.876	2	0.000	0.50	0.000	0.50	-0.003	0.498	-0.001	-0.277	0.484
(5 fams)	D1S2785	0.000	0.50	0.000	0.50	-0.614	0.001	-0.000	-0.819	0.782		0.000	0.50	0.000	0.50	0.011	0.506	0.006	-0.099	0.484
	D1S547	0.000	0.50	0.000	0.50	-0.593	0.001	-0.000	-0.757	0.760		0.000	0.50	0.000	0.50	0.013	0.507	0.007	-0.075	0.484
	D1S1609	0.177	0.00	0.177	0.00	-0.230	0.008	-0.001	-0.328	0.602		0.089	0.00	0.089	0.00	0.025	0.813	0.021	0.086	0.484

* Affected men were considered to have "aggressive disease" if they had high-grade (grade III) or Stage C or D cancer.

† The 5 families with all cases of aggressive disease are included in the group of families with 50 percent or more.

** Excludes families with lod scores < 0.1 at D1S518, DXS984, and D1S407.

TABLE 2-15. LOD SCORES AT *HPCX*, ALL FAMILIES

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*				Multipoint*				
Fams.	Marker	Maxlo	θ	Hlod	θ	lod	α	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-
149 Fam	DXS984	0.16	0.34	0.16	0.34	-6.589	0.004	-0.005	0.395	0.339	78	0.198	0.26	0.341	0.00	-1.849	0.257	0.142	0.761	0.219
	DXS8106	0.00	0.50	0.00	0.50	-9.068	0.002	-0.003	-0.290	0.606		0.000	0.50	0.000	0.50	-4.076	0.006	-0.004	-0.272	0.596
	DXS6806	0.00	0.50	0.00	0.50	-9.469	0.001	-0.003	-0.568	0.709		0.003	0.46	0.003	0.46	-4.403	0.002	-0.002	-0.527	0.693
	DXS1200	0.00	0.50	0.34	0.00	-9.570	0.003	-0.004	-0.125	0.541		0.000	0.50	0.000	0.50	-4.689	0.001	-0.001	-0.465	0.670
	DXS297	0.00	0.50	0.00	0.50	-9.948	0.001	-0.002	-0.407	0.651		0.006	0.46	0.006	0.46	-4.695	0.001	-0.001	-0.508	0.686
	DXS1193	0.04	0.44	0.04	0.44	-11.917	0.000	-0.001	-0.888	0.811		0.000	0.50	0.016	0.00	-3.912	0.037	-0.001	0.100	0.448
	DXS8069	0.00	0.50	0.00	0.50	-12.355	0.000	-0.001	-1.230	0.892		0.000	0.50	0.022	0.00	-4.012	0.035	-0.002	0.020	0.480
	DXS8103	0.00	0.50	0.00	0.50	-13.539	0.000	-0.001	-1.604	0.949		0.058	0.40	0.058	0.40	-3.767	0.040	-0.001	-0.036	0.503

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

TABLE 2-16. LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY PUTATIVE INHERITANCE PATTERN

									Excluding Families with Possible Linkage to Other Loci**									
		2point*		Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod(θ)	Hlod (θ)	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
Male-to-Male	DXS984	0.02 (0.42)	0.02 (0.42)	-2.221	0.032	-0.007	0.839	0.198	39	0.068	0.30	0.068	0.30	-0.935	0.196	0.016	-0.022	0.480
(82 families)	DXS8106	0 (0.50)	0 (0.50)	-2.285	0.189	0.124	0.751	0.222		0.000	0.50	0.000	0.50	-1.552	0.006	-0.002	-0.883	0.795
	DXS6806	0 (0.50)	0 (0.50)	-2.581	0.152	0.093	0.417	0.330		0.000	0.50	0.000	0.50	-1.409	0.004	-0.002	-1.005	0.846
	DXS1200	0 (0.50)	0.02 (0.00)	-3.858	0.055	0.001	0.211	0.406		0.000	0.50	0.000	0.50	-1.527	0.001	-0.001	-0.659	0.753
	DXS297	0 (0.50)	0.01 (0.00)	-3.800	0.034	-0.005	0.108	0.446		0.000	0.50	0.000	0.50	-1.349	0.001	-0.001	-0.597	0.726
	DXS1193	0.00 (0.46)	0.00 (0.46)	-5.496	0.000	-0.001	-0.402	0.647		0.000	0.50	0.000	0.50	-0.847	0.005	-0.002	-0.419	0.634
	DXS8069	0 (0.50)	0 (0.50)	-5.795	0.000	-0.001	-0.910	0.817		0.006	0.46	0.006	0.46	-0.766	0.008	-0.003	-0.280	0.605
	DXS8103	0 (0.50)	0 (0.50)	-6.613	0.000	-0.000	-1.370	0.918		0.009	0.46	0.012	0.00	-0.858	0.006	-0.002	-0.361	0.618
Non Male-to-	DXS984	0.08 (0.24)	0.09 (0.00)	-1.493	0.002	-0.001	-0.001	0.467	7	0.703	0.00	0.703	0.00	0.149	0.621	0.207	0.607	0.261
Male	DXS8106	0 (0.50)	0 (0.50)	-2.071	0.000	-0.000	-0.362	0.607		0.000	0.50	0.000	0.50	-0.285	0.174	0.004	0.166	0.372
(17 families)	DXS6806	0.09 (0.30)	0.10 (0.30)	-2.399	0.000	-0.000	-0.450	0.645		0.096	0.24	0.096	0.24	-0.603	0.015	-0.002	0.061	0.403
	DXS1200	0.05 (0.24)	0.10 (0.30)	-2.366	0.000	-0.000	-0.345	0.600		0.001	0.46	0.001	0.46	-0.573	0.022	-0.002	0.059	0.403
	DXS297	0 (0.50)	0.00 (0.30)	-2.397	0.000	-0.000	-0.342	0.599		0.066	0.26	0.066	0.26	-0.572	0.023	-0.002	0.061	0.403
	DXS1193	0.03 (0.18)	0.11 (0.00)	-2.273	0.000	-0.000	-0.327	0.593		0.313	0.00	0.324	0.00	-0.491	0.038	-0.002	0.065	0.401
	DXS8069	0 (0.50)	0 (0.50)	-2.270	0.000	-0.000	-0.326	0.592		0.209	0.00	0.261	0.00	-0.495	0.037	-0.002	0.064	0.401
	DXS8103	0.17 (0.26)	0.17 (0.26)	-2.616	0.000	-0.000	-0.380	0.615		0.251	0.18	0.251	0.18	-0.513	0.033	-0.002	0.070	0.401
Siblings Only	DXS984	0.24 (0.22)	0.33 (0.00)	-1.797	0.081	-0.002	-0.206	0.569	29	0.017	0.30	0.069	0.00	-0.935	0.196	0.016	-0.022	0.480
(44 families)	DXS8106	0 (0.50)	0 (0.50)	-3.160	0.001	-0.001	-1.213	0.890		0.000	0.50	0.000	0.50	-1.552	0.006	-0.002	-0.883	0.795
	DXS6806	0 (0.50)	0 (0.50)	-2.945	0.001	-0.001	-1.254	0.898		0.000	0.50	0.000	0.50	-1.409	0.004	-0.002	-1.005	0.846
	DXS1200	0.40 (0.16)	0.40 (0.16)	-1.835	0.093	0.011	-0.394	0.641		0.000	0.50	0.000	0.50	-1.527	0.001	-0.001	-0.659	0.753
	DXS297	0 (0.50)	0 (0.50)	-2.239	0.013	-0.004	-0.747	0.767		0.000	0.50	0.000	0.50	-1.349	0.001	-0.001	-0.597	0.726
	DXS1193	0 (0.50)	0 (0.50)	-2.574	0.001	-0.001	-0.963	0.829		0.030	0.24	0.030	0.24	-0.847	0.005	-0.002	-0.419	0.634
	DXS8069	0.02 (0.28)	0.02 (0.28)	-2.718	0.001	-0.001	-0.933	0.822		0.000	0.50	0.000	0.50	-0.766	0.008	-0.003	-0.280	0.605
	DXS8103	0 (0.50)	0 (0.50)	-2.762	0.001	-0.001	-0.982	0.834		0.000	0.42	0.000	0.42	-0.858	0.006	-0.002	-0.361	0.618
Non Male-to	DXS984	0.32 (0.22)	0.41 (0.00)	-3.290	0.013	-0.005	-0.182	0.559	36	0.330	0.14	0.569	0.00	-0.786	0.354	0.149	0.247	0.387
Male and	DXS8106	0 (0.50)	0 (0.50)	-5.231	0.000	-0.001	-1.238	0.895		0.000	0.50	0.000	0.50	-1.838	0.013	-0.004	-0.719	0.758

TABLE 2-16 (CONTINUED). LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY PUTATIVE INHERITANCE PATTERN

		2point*		Multipoint*					Excluding Families with Possible Linkage to Other Loci**								
									2point*				Multipoint*				
Fams.	Marker	Maxlod(θ)	Hlod (θ)	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
Siblings only	DXS6806	0.02 (0.44)	0.02 (0.44)	-5.344	0.000	-0.001	-1.316	0.909		0.014	0.44	0.014	0.44	-2.012	0.003	-0.002	-0.874	0.802
(65 families)	DXS1200	0.44 (0.18)	0.44 (0.18)	-4.201	0.003	-0.003	-0.511	0.686		0.001	0.46	0.001	0.46	-2.101	0.001	-0.001	-0.566	0.702
	DXS297	0 (0.50)	0 (0.50)	-4.637	0.001	-0.001	-0.820	0.790		0.049	0.30	0.049	0.30	-1.922	0.001	-0.001	-0.509	0.680
	DXS1193	0.03 (0.00)	0.03 (0.00)	-4.848	0.000	-0.001	-1.001	0.841		0.195	0.08	0.265	0.00	-1.339	0.005	-0.002	-0.347	0.622
	DXS8069	0.03 (0.06)	0.03 (0.06)	-4.988	0.000	-0.000	-0.975	0.834		0.067	0.14	0.157	0.00	-1.261	0.007	-0.003	-0.223	0.573
	DXS8103	0.04 (0.42)	0.04 (0.42)	-5.378	0.000	-0.000	-1.044	0.852		0.184	0.26	0.184	0.26	-1.371	0.006	-0.003	-0.293	0.601

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

TABLE 2-17. LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY MEDIAN AGE AT DIAGNOSIS

											Excluding Families with Possible Linkage to Other Loci**									
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod	Θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
< 60 years	DXS984	0.000	0.50	0.000	0.50	-1.647	0.000	-0.000	-0.365	0.648	3	0.027	0.00	0.027	0.00	0.159	0.996	0.159	1.343	0.125
(13 families)	DXS8106	0.000	0.50	0.000	0.50	-1.826	0.068	0.006	0.198	0.436		0.274	0.00	0.274	0.00	0.190	0.997	0.190	1.629	0.125
	DXS6806	0.110	0.26	0.131	0.00	-1.795	0.096	0.022	0.191	0.436		0.120	0.00	0.120	0.00	0.153	0.995	0.152	1.331	0.125
	DXS1200	0.000	0.46	0.001	0.46	-2.330	0.000	-0.000	-1.144	0.887		0.000	0.50	0.000	0.50	-0.122	0.009	-0.001	-0.593	0.875
	DXS297	0.000	0.50	0.000	0.50	-2.396	0.000	-0.000	-1.209	0.890		0.000	0.50	0.000	0.50	-0.122	0.009	-0.001	-0.592	0.875
	DXS1193	0.000	0.50	0.000	0.50	-3.408	0.000	-0.000	-1.588	0.955		0.000	0.50	0.000	0.50	-0.122	0.010	-0.001	-0.596	0.875
	DXS8069	0.000	0.50	0.000	0.50	-3.529	0.000	-0.000	-1.608	0.967		0.027	0.00	0.027	0.00	-0.122	0.009	-0.001	-0.593	0.875
	DXS8103	0.000	0.50	0.000	0.50	-3.618	0.000	-0.000	-1.627	0.967		0.000	0.50	0.000	0.50	-0.124	0.009	-0.001	-0.612	0.875
60-64 years	DXS984	0.790	0.10	1.015	0.00	-1.828	0.098	0.004	1.274	0.105	15	0.499	0.08	0.737	0.00	-0.461	0.447	0.175	1.134	0.131
(33 families)	DXS8106	0.000	0.50	0.000	0.50	-3.387	0.000	-0.000	0.276	0.377		0.000	0.50	0.000	0.50	-1.160	0.039	-0.003	0.393	0.330
	DXS6806	0.010	0.44	0.010	0.44	-3.413	0.000	-0.000	0.332	0.357		0.024	0.42	0.024	0.42	-1.286	0.005	-0.001	0.472	0.304
	DXS1200	0.029	0.32	0.029	0.32	-3.164	0.000	-0.000	0.153	0.423		0.005	0.46	0.005	0.46	-1.267	0.004	-0.001	0.113	0.429
	DXS297	0.003	0.46	0.003	0.46	-3.002	0.000	-0.000	0.080	0.452		0.008	0.40	0.008	0.40	-1.120	0.004	-0.001	-0.000	0.470
	DXS1193	0.257	0.16	0.310	0.00	-1.688	0.106	0.036	0.933	0.173		1.136	0.00	1.136	0.00	0.192	0.503	0.397	1.319	0.099
	DXS8069	0.473	0.06	0.511	0.00	-1.608	0.111	0.039	0.656	0.249		0.686	0.00	0.686	0.00	0.214	0.512	0.411	1.387	0.089
	DXS8103	0.338	0.24	0.338	0.24	-1.650	0.110	0.038	0.704	0.234		0.671	0.12	0.671	0.12	0.122	0.499	0.384	1.451	0.080
65-69 years	DXS984	0.000	0.50	0.000	0.50	-1.769	0.052	-0.005	0.198	0.407	25	0.000	0.50	0.000	0.50	-0.152	0.445	0.173	0.576	0.270
(55 families)	DXS8106	0.000	0.50	0.000	0.50	-2.075	0.022	-0.005	0.119	0.437		0.004	0.40	0.004	0.40	-0.792	0.147	0.012	0.226	0.390
	DXS6806	0.000	0.50	0.000	0.50	-2.471	0.005	-0.003	-0.034	0.498		0.000	0.50	0.000	0.50	-0.864	0.128	0.007	0.263	0.377
	DXS1200	0.044	0.26	0.174	0.00	-2.476	0.148	0.062	0.740	0.224		0.000	0.50	0.006	0.06	-0.887	0.117	0.004	0.325	0.357
	DXS297	0.000	0.50	0.000	0.50	-2.824	0.059	0.001	0.332	0.357		0.003	0.46	0.003	0.46	-1.018	0.072	-0.003	0.295	0.367
	DXS1193	0.000	0.50	0.000	0.50	-4.245	0.000	-0.001	-0.469	0.668		0.000	0.50	0.000	0.50	-1.529	0.003	-0.001	0.297	0.367
	DXS8069	0.000	0.50	0.000	0.50	-4.662	0.000	-0.000	-0.673	0.741		0.000	0.50	0.000	0.50	-1.625	0.002	-0.001	0.309	0.362
	DXS8103	0.000	0.50	0.000	0.50	-5.063	0.000	-0.000	-0.789	0.779		0.000	0.50	0.000	0.50	-1.608	0.002	-0.001	0.300	0.365

TABLE 2-17 (CONTINUED). LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY MEDIAN AGE AT DIAGNOSIS

											Excluding Families with Possible Linkage to Other Loci**									
		2point*				Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod	Θ	Hlod	θ	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
70+ years	DXS984	0.084	0.22	0.084	0.22	0.112	0.501	0.174	-0.265	0.591	32	0.190	0.14	0.190	0.14	-0.211	0.191	-0.007	-0.267	0.584
(42 families)	DXS8106	0.000	0.50	0.000	0.50	-0.013	0.488	0.140	-1.096	0.864		0.000	0.50	0.000	0.50	-0.946	0.006	-0.002	-1.424	0.926
	DXS6806	0.000	0.50	0.000	0.50	-0.107	0.404	0.106	-1.531	0.944		0.000	0.50	0.000	0.50	-1.043	0.004	-0.002	-1.845	0.974
	DXS1200	0.257	0.08	0.331	0.00	0.057	0.499	0.162	-0.708	0.754		0.000	0.50	0.000	0.50	-1.068	0.002	-0.001	-1.044	0.848
	DXS297	0.299	0.06	0.325	0.00	-0.067	0.431	0.116	-0.682	0.745		0.000	0.50	0.000	0.50	-1.092	0.002	-0.001	-1.015	0.840
	DXS1193	0.498	0.00	0.498	0.00	-0.111	0.395	0.105	-0.724	0.759		0.000	0.50	0.000	0.50	-1.110	0.002	-0.001	-0.984	0.835
	DXS8069	0.022	0.26	0.155	0.00	-0.094	0.408	0.109	-0.870	0.803		0.000	0.50	0.000	0.50	-1.136	0.002	-0.001	-1.171	0.881
	DXS8103	0.000	0.50	0.000	0.50	-0.780	0.004	-0.002	-1.473	0.935		0.000	0.50	0.000	0.50	-0.823	0.002	-0.002	-1.290	0.909

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

TABLE 2-18. LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY DISTRIBUTION OF TUMOR GRADE

									Excluding Families with Possible Linkage to Other Loci***								
		2point*		Multipoint*					2point*					Multipoint*			
Fams.	Marker	Maxlod(θ)	Hlod (θ)	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
All low grade	DXS984	0 (0.50)	0 (0.50)	-0.639	0.167	0.006	0.526	0.292	29	0.010	0.30	0.090	0.00	0.476	0.877	0.469	1.116	0.133
or both low	DXS8106	0 (0.50)	0 (0.50)	-2.409	0.002	-0.002	-0.685	0.748		0.000	0.50	0.000	0.00	-0.151	0.395	0.061	-0.255	0.601
and moderate	DXS6806	0 (0.50)	0 (0.50)	-2.545	0.001	-0.001	-0.789	0.780		0.000	0.50	0.000	0.50	-0.164	0.381	0.055	-0.276	0.610
Grade **	DXS1200	0.05 (0.18)	0.05 (0.18)	-2.513	0.001	-0.001	-0.669	0.742		0.027	0.22	0.031	0.06	-0.140	0.410	0.065	-0.165	0.554
(48 families)	DXS297	0 (0.50)	0 (0.50)	-2.741	0.001	-0.001	-0.758	0.770		0.000	0.50	0.000	0.50	-0.227	0.322	0.030	-0.280	0.611
	DXS1193	0 (0.50)	0 (0.50)	-3.901	0.000	-0.000	-1.090	0.862		0.000	0.50	0.000	0.50	-0.961	0.005	-0.002	-0.630	0.735
	DXS8069	0 (0.50)	0 (0.50)	-4.042	0.000	-0.000	-1.452	0.931		0.000	0.50	0.000	0.50	-1.113	0.003	-0.002	-0.704	0.765
	DXS8103	0 (0.50)	0 (0.50)	-4.125	0.000	-0.000	-1.567	0.946		0.000	0.50	0.000	0.50	-1.169	0.002	-0.001	-0.853	0.790
All moderate	DXS984	0.02 (0.42)	0.02 (0.42)	-3.776	0.001	-0.001	0.081	0.455	28	0.000	0.50	0.005	0.00	-1.276	0.053	-0.005	0.140	0.424
Grade	DXS8106	0 (0.50)	0.00 (0.46)	-3.481	0.054	0.002	0.396	0.336		0.000	0.50	0.000	0.50	-1.653	0.007	-0.003	-0.021	0.491
(58 families)	DXS6806	0.12 (0.30)	0.12 (0.30)	-3.511	0.048	0.002	0.281	0.378		0.000	0.50	0.000	0.50	-1.508	0.006	-0.002	-0.006	0.485
	DXS1200	0.13 (0.26)	0.18 (0.00)	-3.513	0.088	0.021	0.541	0.286		0.000	0.50	0.000	0.50	-1.551	0.003	-0.002	-0.090	0.521
	DXS297	0 (0.50)	0 (0.50)	-3.713	0.020	-0.005	0.124	0.438		0.001	0.46	0.001	0.46	-1.509	0.003	-0.002	-0.130	0.536
	DXS1193	0 (0.50)	0 (0.50)	-4.450	0.000	-0.001	-0.208	0.570		0.000	0.50	0.000	0.50	-0.894	0.045	-0.005	0.506	0.294
	DXS8069	0.00 (0.46)	0.00 (0.46)	-4.871	0.000	-0.001	-0.495	0.680		0.000	0.50	0.000	0.50	-0.909	0.045	-0.005	0.312	0.365
	DXS8103	0.01 (0.46)	0.01 (0.46)	-4.989	0.000	-0.001	-0.550	0.700		0.004	0.44	0.004	0.44	-0.990	0.034	-0.005	0.305	0.367
At least 1	DXS984	0.48 (0.18)	0.48 (0.18)	-1.546	0.083	0.003	-0.021	0.489	18	0.654	0.08	0.654	0.08	0.134	0.543	0.238	0.314	0.353
high-grade	DXS8106	0 (0.50)	0 (0.50)	-2.551	0.003	-0.002	-0.514	0.683		0.000	0.50	0.027	0.00	-0.904	0.034	-0.004	-0.257	0.573
(37 families)	DXS6806	0.01 (0.44)	0.01 (0.44)	-2.846	0.001	-0.001	-0.791	0.779		0.026	0.40	0.026	0.40	-1.368	0.002	-0.001	-0.816	0.784
	DXS1200	0.00 (0.44)	0.01 (0.00)	-3.019	0.002	-0.001	-0.469	0.666		0.003	0.48	0.003	0.48	-1.653	0.000	-0.000	-0.824	0.787
	DXS297	0.00 (0.38)	0.03 (0.00)	-2.936	0.002	-0.001	-0.371	0.628		0.017	0.36	0.017	0.36	-1.616	0.000	-0.000	-0.730	0.757
	DXS1193	0.06 (0.26)	0.19 (0.00)	-2.052	0.139	0.083	0.156	0.419		0.661	0.00	0.663	0.00	-0.713	0.229	0.117	0.167	0.406
	DXS8069	0.04 (0.22)	0.30 (0.00)	-1.930	0.152	0.097	0.280	0.373		0.145	0.14	0.270	0.00	-0.646	0.250	0.134	0.329	0.347
	DXS8103	0.08 (0.38)	0.08 (0.38)	-2.562	0.035	-0.000	-0.222	0.569		0.444	0.18	0.444	0.18	-0.272	0.325	0.182	0.409	0.321

* Parametric analyses used Model b+.

** Represents grade of prostatectomy specimen, when available, otherwise, grade from biopsy specimen.

*** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

TABLE 2-19. LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY CANCER STAGE

									Excluding Families with Possible Linkage to Other Loci**									
		2point*		Multipoint*					2point*					Multipoint*				
Fams.	Marker	Maxlod(θ)	Hlod (θ)	lod	α	hlod	npl	p-value	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
All local stage	DXS984	0.27 (0.22)	0.27 (0.22)	-1.066	0.353	0.284	0.771	0.216	39	0.448	0.14	0.499	0.02	-0.045	0.548	0.473	0.999	0.159
(63 families)	DXS8106	0 (0.50)	0 (0.50)	-4.024	0.034	-0.005	-0.342	0.623		0.000	0.50	0.000	0.50	-1.550	0.119	0.006	-0.197	0.568
	DXS6806	0.02 (0.44)	0.02 (0.44)	-4.195	0.018	-0.005	-0.278	0.598		0.020	0.44	0.020	0.44	-1.639	0.060	-0.004	-0.137	0.544
	DXS1200	0.05 (0.34)	0.05 (0.34)	-5.267	0.002	-0.002	-0.332	0.619		0.006	0.46	0.006	0.46	-1.906	0.006	-0.003	-0.228	0.579
	DXS297	0.03 (0.38)	0.03 (0.38)	-4.994	0.002	-0.002	-0.383	0.639		0.031	0.36	0.031	0.36	-1.804	0.004	-0.002	-0.264	0.591
	DXS1193	0.28 (0.18)	0.33 (0.00)	-4.487	0.002	-0.002	-0.103	0.529		0.383	0.04	0.383	0.04	-1.838	0.002	-0.002	0.070	0.456
	DXS8069	0.11 (0.22)	0.23 (0.00)	-4.653	0.002	-0.002	-0.607	0.721		0.103	0.18	0.226	0.00	-1.944	0.002	-0.001	-0.231	0.580
	DXS8103	0.04 (0.42)	0.04 (0.42)	-5.076	0.000	-0.001	-1.064	0.856		0.086	0.34	0.086	0.34	-1.742	0.002	-0.002	-0.327	0.611
Local &	DXS984	0.15 (0.42)	0.15 (0.28)	-2.331	0.001	-0.001	-0.067	0.514	22	0.041	0.34	0.041	0.34	-0.601	0.044	-0.005	0.173	0.414
regional ***	DXS8106	0 (0.50)	0 (0.50)	-2.450	0.013	-0.004	-0.615	0.723		0.063	0.18	0.063	0.18	-1.104	0.002	-0.001	-0.820	0.788
(55 families)	DXS6806	0 (0.50)	0 (0.50)	-2.666	0.012	-0.004	-1.173	0.881		0.002	0.46	0.002	0.46	-1.288	0.001	-0.001	-1.380	0.925
	DXS1200	0 (0.50)	0.06 (0.04)	-1.434	0.157	0.053	-0.569	0.707		0.000	0.50	0.000	0.50	-1.366	0.001	-0.001	-1.380	0.925
	DXS297	0.00 (0.44)	0.01 (0.44)	-1.891	0.053	-0.002	-0.841	0.796		0.001	0.46	0.001	0.46	-1.315	0.001	-0.001	-1.260	0.902
	DXS1193	0 (0.50)	0 (0.50)	-4.254	0.000	-0.000	-1.785	0.968		0.000	0.50	0.037	0.00	-0.359	0.289	0.147	-0.402	0.640
	DXS8069	0.01 (0.46)	0.01 (0.46)	-4.578	0.000	-0.000	-1.777	0.967		0.007	0.44	0.007	0.44	-0.243	0.332	0.177	-0.152	0.539
	DXS8103	0.00 (0.46)	0.00 (0.46)	-5.048	0.000	-0.000	-1.902	0.976		0.152	0.22	0.170	0.00	-0.219	0.341	0.182	-0.171	0.547
At least 1	DXS984	0.01 (0.46)	0.01 (0.46)	-2.172	0.000	-0.000	-0.161	0.540	14	0.006	0.44	0.014	0.00	-0.017	0.497	0.065	0.277	0.364
distant stage	DXS8106	0 (0.50)	0 (0.50)	-1.609	0.001	-0.001	0.390	0.330		0.000	0.50	0.002	0.00	-0.054	0.480	0.064	0.669	0.247
(25 families)	DXS6806	0 (0.50)	0 (0.50)	-1.632	0.001	-0.001	0.398	0.327		0.000	0.50	0.000	0.50	-0.113	0.409	0.048	0.626	0.258
	DXS1200	0.13 (0.14)	0.20 (0.00)	-1.934	0.001	-0.001	0.580	0.268		0.408	0.00	0.408	0.00	-0.073	0.454	0.056	0.810	0.204
	DXS297	0 (0.50)	0 (0.50)	-2.128	0.001	-0.001	0.404	0.325		0.000	0.50	0.000	0.50	-0.232	0.293	0.023	0.606	0.262
	DXS1193	0 (0.50)	0 (0.50)	-2.236	0.000	-0.000	0.260	0.376		0.000	0.50	0.000	0.50	-0.370	0.168	0.003	0.385	0.323
	DXS8069	0 (0.50)	0 (0.50)	-2.337	0.000	-0.000	0.253	0.379		0.000	0.50	0.000	0.50	-0.480	0.112	-0.001	0.380	0.324
	DXS8103	0 (0.50)	0 (0.50)	-2.295	0.000	-0.000	0.294	0.364		0.000	0.50	0.000	0.50	-0.471	0.116	-0.001	0.430	0.309

* Parametric analyses used Model b+.

** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

*** Represents pathologic stage, when available, otherwise, clinical stage.

TABLE 2-20. LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY AGGRESSIVE DISEASE

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*				Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
None	DXS984	0.008	0.36	0.009	0.32	-1.692	0.150	0.021	0.355	0.351		0.041	0.24	0.157	0.00	-0.448	0.462	0.191	0.648	0.263
(53 families)	DXS8106	0.000	0.50	0.000	0.50	-3.814	0.002	-0.002	-0.698	0.751		0.000	0.50	0.000	0.50	-1.149	0.137	0.005	-0.505	0.704
	DXS6806	0.000	0.50	0.000	0.50	-3.671	0.002	-0.002	-0.598	0.718		0.000	0.50	0.000	0.50	-0.904	0.160	0.009	-0.378	0.630
	DXS1200	0.000	0.50	0.002	0.00	-4.427	0.001	-0.001	-0.454	0.664		0.000	0.50	0.000	0.50	-0.803	0.173	0.012	-0.139	0.560
	DXS297	0.000	0.50	0.000	0.50	-4.143	0.001	-0.001	-0.518	0.689		0.001	0.44	0.001	0.44	-0.688	0.154	0.004	-0.176	0.563
	DXS1193	0.005	0.38	0.005	0.38	-3.696	0.001	-0.001	-0.184	0.560		0.033	0.20	0.033	0.20	-0.711	0.086	-0.005	0.200	0.410
	DXS8069	0.000	0.50	0.000	0.50	-3.863	0.000	-0.001	-0.722	0.758		0.058	0.16	0.058	0.16	-0.786	0.060	-0.006	-0.120	0.557
	DXS8103	0.000	0.50	0.000	0.50	-3.992	0.000	-0.001	-0.827	0.792		0.000	0.50	0.000	0.50	-0.925	0.032	-0.006	-0.261	0.577
< 50	DXS984	0.293	0.24	0.332	0.02	-0.763	0.289	0.134	1.080	0.141	29	0.129	0.24	0.180	0.00	-0.627	0.205	0.026	0.653	0.247
(59 families)	DXS8106	0.000	0.50	0.000	0.50	-1.311	0.153	0.033	0.895	0.183		0.000	0.50	0.000	0.50	-1.685	0.003	-0.002	0.221	0.393
	DXS6806	0.004	0.46	0.004	0.46	-2.012	0.046	-0.004	0.558	0.281		0.012	0.44	0.012	0.44	-2.139	0.001	-0.001	0.058	0.455
	DXS1200	0.000	0.50	0.031	0.04	-2.560	0.029	-0.005	0.390	0.338		0.002	0.46	0.002	0.46	-2.515	0.000	-0.000	-0.282	0.591
	DXS297	0.006	0.46	0.006	0.46	-3.172	0.004	-0.003	-0.033	0.500		0.003	0.46	0.003	0.46	-2.654	0.000	-0.000	-0.392	0.634
	DXS1193	0.000	0.50	0.000	0.50	-4.101	0.000	-0.001	-0.595	0.716		0.000	0.50	0.000	0.50	-2.652	0.000	-0.000	-0.508	0.678
	DXS8069	0.000	0.50	0.000	0.00	-3.993	0.000	-0.001	-0.568	0.706		0.000	0.50	0.00	0.00	-2.727	0.000	-0.000	-0.421	0.645
	DXS8103	0.006	0.46	0.006	0.46	-5.026	0.000	-0.000	-1.074	0.859		0.024	0.44	0.024	0.44	-2.357	0.000	-0.000	-0.376	0.628
>= 50%	DXS984	0.029	0.42	0.029	0.42	-2.549	0.000	-0.000	-0.910	0.815	13	0.210	0.00	0.210	0.00	0.411	0.991	0.408	0.234	0.362
(31 families)	DXS8106	0.000	0.50	0.000	0.50	-1.851	0.027	-0.003	-0.769	0.772		0.295	0.00	0.295	0.00	0.126	0.698	0.122	-0.239	0.564
	DXS6806	0.011	0.36	0.31	0.00	-1.755	0.049	0.002	-1.045	0.852		0.003	0.44	0.003	0.44	0.002	0.498	0.043	-0.866	0.790
	DXS1200	0.274	0.16	0.320	0.00	-0.587	0.277	0.132	-0.158	0.545		0.000	0.50	0.000	0.50	-0.027	0.496	0.031	-0.706	0.770
	DXS297	0.000	0.50	0.045	0.00	-0.629	0.260	0.098	-0.094	0.520		0.000	0.40	0.000	0.40	-0.010	0.497	0.039	-0.602	0.728
	DXS1193	0.058	0.32	0.058	0.32	-1.271	0.154	0.065	-0.092	0.519		0.466	0.00	0.466	0.00	0.794	0.990	0.792	0.438	0.325
	DXS8069	0.215	0.10	0.215	0.10	-1.674	0.099	0.028	-0.133	0.535		0.328	0.00	0.328	0.00	0.845	0.993	0.843	0.618	0.277
	DXS8103	0.075	0.34	0.075	0.34	-1.746	0.097	0.027	-0.126	0.532		0.690	0.00	0.690	0.00	0.850	0.993	0.848	0.636	0.277
All†	DXS984	0.268	0.00	0.268	0.00	0.020	0.504	0.014	0.946	0.226	3	0.177	0.00	0.177	0.00	0.103	0.987	0.102	0.636	0.250
(5 families)	DXS8106	0.263	0.00	0.263	0.00	-0.137	0.013	-0.001	0.276	0.261		0.024	0.02	0.024	0.02	-0.073	0.035	-0.002	-0.069	0.437

TABLE 2-20 (CONTINUED). LOD SCORES AT *HPCX* WHITE FAMILIES STRATIFIED BY AGGRESSIVE DISEASE

											Excluding Families with Possible Linkage to Other Loci**								
		2point*				Multipoint*					2point*				Multipoint*				
Fams.	Marker	Maxlod	θ	Hlod	θ	lod	α	hlod	npl	p-	Fams	Maxlod	θ	Hlod	θ	lod	α	Hlod	NPL	p-value
	DXS6806	0.000	0.50	0.008	0.00	-0.142	0.012	-0.001	0.220	0.472		0.056	0.00	0.056	0.00	-0.075	0.031	-0.002	-0.098	0.718
	DXS1200	0.221	0.00	0.221	0.00	-0.059	0.121	-0.005	1.100	0.226		0.000	0.50	0.000	0.50	0.004	0.501	0.006	0.998	0.250
	DXS297	0.030	0.14	0.031	0.00	-0.057	0.135	-0.005	1.131	0.226		0.000	0.50	0.000	0.50	0.007	0.502	0.008	1.051	0.250
	DXS1193	0.000	0.50	0.000	0.50	-0.058	0.132	-0.005	1.131	0.226		0.005	0.14	0.005	0.08	0.009	0.503	0.009	1.076	0.250
	DXS8069	0.000	0.50	0.000	0.50	-0.060	0.120	-0.005	1.114	0.226		0.129	0.00	0.129	0.00	0.008	0.503	0.009	1.068	0.250
	DXS8103	0.029	0.14	0.030	0.00	-0.062	0.110	-0.004	1.094	0.226		0.000	0.50	0.000	0.50	0.007	0.502	0.008	1.045	0.250

* Affected men were considered to have "aggressive disease" if they had high-grade (grade III) or Stage C or D cancer.
† The 5 families with all cases of aggressive disease are included in the group of families with 50 percent or more.
** Excludes families with lod scores < 0.1 at D1S518, D1S2785, and D1S407.

TABLE 2-21. LOD SCORES AT *CAPB*

									Excluding Families with Possible Linkage to Other Loci†									
		No.		2-point*		Multipoint*			No.	2-point*				Multipoint*				
		Fam.	Marker	MaxLod (θ)	Lod	Hlod (α)	NPL (p-value)		Fam.	Maxlod	θ	Hold	θ	Lod	α	hlod	npl	p-value
All Families		149	D1S1597	0.16 (0.30)	-6.60	0.15 (0.15)	1.44 (0.08)		78	0.612	0.12	0.800	0.00	0.347	0.54	0.866	2.045	0.023
			D1S407	0.86 (0.18)	-5.43	0.21 (0.18)	1.50 (0.07)			0.368	0.16	0.508	0.00	-0.228	0.48	0.622	1.982	0.027
White,	< 60 yrs	13	D1S1597	0 (0.50)	-2.27	-0.00 (0.00)	0.04 (0.47)		5	0.469	0.00	0.469	0.00	0.388	0.996	0.387	0.796	0.213
Median Age			D1S407	0.06 (0.22)	-1.66	-0.00 (0.00)	0.04 (0.47)			0.190	0.00	0.190	0.00	0.368	0.994	0.367	0.732	0.239
At Diagnosis	60-64 yrs	34	D1S1597	0.75 (0.10)	0.51	0.89 (0.59)	1.36 (0.09)		15	0.222	0.10	0.274	0.00	0.947	0.996	0.946	1.736	0.049
			D1S407	0.81 (0.10)	0.29	0.76 (0.54)	1.35 (0.09)			0.392	0.10	0.392	0.10	0.565	0.793	0.595	1.624	0.059
	65-69 yrs	54	D1S1597	0.02 (0.44)	-5.43	-0.00 (0.00)	-0.25 (0.59)		25	0.038	0.28	0.061	0.04	-0.881	0.128	0.006	0.268	0.379
			D1S407	0.20 (0.24)	-4.62	-0.00 (0.00)	-0.22 (0.57)			0.056	0.22	0.166	0.00	-1.124	0.058	-0.004	0.183	0.412
	70+ yrs	42	D1S1597	0.00 (0.48)	-0.13	0.08 (0.48)	1.45 (0.08)		30	0.116	0.00	0.116	0.00	0.065	0.509	0.107	1.435	0.079
			D1S407	0 (0.50)	-0.22	0.05 (0.40)	1.54 (0.07)			0.000	0.50	0.001	0.00	0.040	0.502	0.095	1.539	0.066
White,	Low/medium	49	D1S1597	0 (0.50)	-3.02	-0.00 (0.00)	0.30 (0.37)		27	0.000	0.50	0.000	0.00	-0.332	0.206	-0.000	0.865	0.192
grade**			D1S407	0.26 (0.18)	-2.26	-0.00 (0.00)	0.49 (0.34)			0.000	0.50	0.000	0.00	-0.426	0.096	-0.007	0.866	0.192
	Medium	57	D1S1597	0.12 (0.30)	-4.51	0.02 (0.07)	0.32 (0.36)		31	0.095	0.22	0.095	0.22	-0.722	0.192	0.028	0.534	0.288
			D1S407	0.23 (0.22)	-4.04	0.01 (0.07)	0.33 (0.36)			0.079	0.22	0.175	0.00	-1.148	0.120	0.008	0.534	0.288
	At least 1high	37	D1S1597	0.42 (0.12)	0.20	0.57 (0.55)	1.82 (0.04)		17	1.239	0.00	1.239	0.00	1.576	0.999	1.576	2.440	0.011
			D1S407	0.16 (0.22)	0.10	0.55 (0.52)	1.83 (0.04)			0.769	0.00	0.769	0.00	1.424	0.998	1.424	2.336	0.014
White,	Local	63	D1S1597	0 (0.50)	-3.80	-0.01 (0.02)	0.97 (0.17)		39	0.237	0.14	0.283	0.00	0.587	0.750	0.627	1.682	0.050
Stage***			D1S407	0.14 (0.22)	-2.63	-0.00 (0.07)	1.15 (0.13)			0.377	0.00	0.381	0.00	0.666	0.806	0.681	1.767	0.042
	Local/regional	55	D1S1597	0.27 (0.24)	-2.56	0.03 (0.13)	0.57 (0.28)		22	1.075	0.00	1.075	0.00	1.199	0.998	1.198	1.407	0.084
			D1S407	0.12 (0.28)	-2.13	0.08 (0.19)	0.53 (0.29)			0.421	0.02	0.421	0.02	1.033	0.996	1.032	1.310	0.098
	At least 1 distant	25	D1S1597	0 (0.50)	-0.96	0.07 (0.18)	0.74 (0.22)		14	0.000	0.50	0.000	0.50	-1.265	0.001	-0.000	0.136	0.422
			D1S407	0.48 (0.14)	-1.44	0.02 (0.12)	0.67 (0.24)			0.020	0.32	0.055	0.00	-1.850	0.000	-0.000	0.005	0.473

* Parametric analyses used Model b+

** Represents grade of prostatectomy specimen, when available, otherwise, grade from biopsy specimen.

† Excludes families with lod scores < 0.1 at D1S518, D1S2785, and DXS984.
*** Represents pathologic stage, when available, otherwise, clinical stage.

TABLE 2-22. LOD SCORES AT *CAPB* WHITE FAMILIES STRATIFIED BY AGGRESSIVE DISEASE*

													Excluding Families with Possible Linkage to Other Loci**								
	No.		2pt				Mpt					No.	2pt				Mpt				
Agg Dis	Fa	Marker	Maxlod	θ	Hold	θ	Lod	α	hlod	npl	p-	Fam	Maxlod	θ	Hold	θ	Lod	α	hlod	npl	p-
None	53	D1S1597	0	0.50	0	0.50	-3.85	0.00	-0.00	0.40	0.34	34	0.140	0.18	0.168	0.00	0.365	0.671	0.422	1.247	0.109
		D1S407	0.18	0.18	0.20	0.00	-2.59	0.02	-0.01	0.61	0.27		0.151	0.00	0.198	0.00	0.455	0.742	0.480	1.360	0.090
< 50%	59	D1S1597	0.09	0.30	0.09	0.30	-2.15	0.16	0.04	1.13	0.13	26	0.025	0.26	0.088	0.00	-0.484	0.256	0.038	1.044	0.148
		D1S407	0.09	0.28	0.18	0.00	-2.43	0.16	0.04	1.02	0.15		0.000	0.50	0.009	0.00	-1.285	0.037	-0.005	0.924	0.175
>=50%	31	D1S1597	0.28	0.16	0.32	0.00	-1.32	0.21	0.13	0.73	0.23	15	0.691	0.00	0.691	0.00	0.641	0.97	0.637	1.289	0.102
		D1S407	0.47	0.14	0.47	0.14	-1.18	0.23	0.13	0.74	0.23		0.993	0.00	0.993	0.00	0.681	0.98	0.678	1.171	0.123
All†	5	D1S1597	0.03	0.14	0.03	0.14	0.13	0.74	0.13	0.82	0.21	4	0.279	0.00	0.279	0.00	0.408	0.999	0.407	1.303	0.105
		D1S407	0.17	0.02	0.17	0.02	0.14	0.76	0.15	0.83	0.20		0.425	0.00	0.425	0.00	0.422	0.998	0.422	1.310	0.105

* Affected men were considered to have "aggressive disease" if they had high-grade (grade III) or Stage C or D cancer.

**Excludes families with lod scores < 0.1 at D1S518, D1S2785, and DXS984.

† The 5 families with all cases of aggressive disease are included in the group of families with 50 percent or more.

TABLE 2-23. POWER ANALYSIS OF WHITE FAMILIES WITH MEAN AGE OF DIAGNOSIS <65 YEARS

Percent Linked <65	Percent Linked Total Data Set	θ	Expected Lod	Probability Lod >1	Probability Lod >1.5	Probability Lod > 2	Probability Lod >3
100	50%	0	11.448	1.000	1.000	1.000	1.000
		0.05	7.264	0.999	0.996	0.993	0.975
90	45%	0	7.264	0.999	0.996	0.993	0.975
		0.05	4.751	0.988	0.956	0.905	0.816
80	40%	0	4.581	0.988	0.952	0.890	0.789
		0.05	3.132	0.929	0.832	0.684	0.495
70	35%	0	2.741	0.908	0.744	0.590	0.399
		0.05	1.915	0.749	0.542	0.353	0.202

* 114 families, 1,000 replications, polymorphisms information content = 0.70

TABLE 2-24. POWER ANALYSIS OF WHITE FAMILIES WITH MEAN AGE OF DIAGNOSIS ≥65 YEARS

Number of Families	Linked %	θ	Max lod	probability lod >1	probability lod > 2	probability lod > 3
116	90	0	9.362	1.000	0.999	0.998
		0.05	6.124	1.000	0.977	0.931
116	80	0	5.915	1.000	0.976	0.923
		0.05	4.030	0.981	0.850	0.699
116	70	0	3.585	0.971	0.762	0.578
		0.05	2.441	0.876	0.515	0.290
116	60	0	2.064	0.796	0.402	0.212
		0.05	1.443	0.643	0.220	0.081
58	100	0	7.071	0.999	0.995	0.972
		0.05	4.608	0.992	0.932	0.770
58	90	0	4.608	0.992	0.932	0.770
		0.05	3.127	0.922	0.761	0.473
58	80	0	3.100	0.912	0.730	0.451
		0.05	2.111	0.754	0.472	0.221
58	70	0	1.833	0.663	0.413	0.161
		0.05	1.294	0.510	0.240	0.077

* 1,000 replications, polymorphisms information content = 0.70

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APPENDIX A. PUBLISHED *HPC1* LINKAGE ANALYSIS (CHAPTER 1)

Linkage Analysis of 150 High-Risk Prostate Cancer Families at 1q24-25

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Confirmation of linkage and estimation of the proportion of families who are linked in large independent datasets is essential to understanding the significance of cancer susceptibility genes. We report here on an analysis of 150 high-risk prostate cancer families (2,176 individuals) for potential linkage to the *HPC1* prostate cancer susceptibility locus at 1q24-25. This dataset includes 640 affected men with an average age at prostate cancer diagnosis of 66.8 years (range, 39–94), representing the largest collection of high-risk families analyzed for linkage in this region to date. Linkage to multiple 1q24-25 markers was strongly rejected for the sample as a whole (lod scores at theta = 0 ranged from −30.83 to −18.42). Assuming heterogeneity, the estimated proportion of families linked (al-

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pha) at *HPC1* in the entire dataset was 2.6%, using multipoint analysis. Because locus heterogeneity may lead to false rejection of linkage, data were stratified based on homogeneous subsets. When restricted to 21 Caucasian families with five or more affected family members and mean age at diagnosis < = 65 years, the lod scores at theta = 0 remained less than –4.0. These results indicate that the overall portion of hereditary prostate cancer families whose disease is due to inherited variation in *HPC1* may be less than originally estimated. Genet. Epidemiol. 18:251–275, 2000.

Key words: chromosome 1q; *HPC1*; tumor suppressor

INTRODUCTION

Prostate cancer is a significant cause of morbidity and mortality. In 1999, an estimated 179,300 new prostate cancer cases will be diagnosed, and 37,000 deaths due to the disease will occur in the United States [Landis et al., 1999]. The incidence of prostate cancer varies with age and race. Prostate cancer incidence increases with age; >75% of all cases are diagnosed in men over age 65 years [American Cancer Society, 1999]. African-American men have the highest rate of prostate cancer in the world [American Cancer Society, 1999].

Numerous types of epidemiologic studies support the existence of a genetic component to prostate cancer susceptibility. Migrant studies, for instance, have indicated that genetic factors, in addition to environmental factors, contribute to prostate cancer risk. These studies demonstrated decreased standardized morbidity ratios for prostate cancer among foreign-born compared to native-born U.S. males ranging from 89:100 to 40:100 [Haenszel, 1961; Staszewski and Haenszel, 1965; Haenszel and Kurihara, 1968; Wynder et al., 1971]. Twin studies also suggest that genetics plays a role in prostate cancer risk; higher concordance rates were found for prostate cancer in monozygotic twins (19–27%) than dizygotic twins (4–7%) [Grönberg et al., 1994; Page et al., 1997]. Case-control and cohort studies of familial aggregation show that prostate cancer tends to cluster in families and have suggested two- to threefold increased risks for first-degree relatives of prostate cancer patients [Fincham et al., 1990; Spitz et al., 1991; Whittemore et al., 1995; Grönberg et al., 1996]. Furthermore, significant relative risks have been observed as high as 5.97 for men with a brother affected at <65 years of age [Cannon et al., 1982] and 10.9 for men with three or more affected first-degree relatives [Steinberg et al., 1990]. Some studies also showed that risk of prostate cancer is increased more in men with affected brothers than in men with affected fathers, consistent with X-linked or autosomal recessive modes of inheritance [Hayes et al., 1995; Monroe et al., 1995; Whittemore et al., 1995]. These studies provide the framework for further investigations of inherited prostate cancer susceptibility.

Complex Segregation Analyses

Several complex segregation analyses (CSAs) were performed to assess whether the observed familial clustering of prostate cancer was consistent with Mendelian inheritance. Each of these CSAs supported the existence of an autosomal dominant prostate cancer susceptibility locus. CSA does not distinguish between one or sev-

eral loci with similar effects, thus, the existence of more than one autosomal dominant prostate cancer susceptibility locus is compatible with the CSA results. Carter et al. [1992] studied 691 families ascertained through consecutive prostatectomy patients at Johns Hopkins University. Results of this study showed evidence for the dominant transmission of a rare ($q = 0.003$) high-risk allele with estimated cumulative risk of prostate cancer for carriers of 88% by age 85 years. A more recent CSA was performed on a population-based sample of 2,857 nuclear families ascertained through cases in the Swedish Cancer Register who had sons currently living in Sweden [Grönberg et al., 1997a]. Although it may be important that a general model was not tested [Jarvik, 1998], a dominant model provided the best fit of all major gene models [Grönberg et al., 1997a]. It was estimated that a high-risk allele with a high population frequency ($q = 0.0167$) was responsible for 23% of prostate cancers among carriers by age 65 years and 63% of prostate cancers among carriers by age 85 years. A third CSA was performed on 4,288 nuclear families ascertained through radical prostatectomy cases at the Mayo Clinic [Schaid et al., 1998]. Support for an autosomal dominant model in this analysis was strongest in families with a proband diagnosed under the age of 60 years. Results suggested that the risk of prostate cancer by age 85 years was 89% for carriers of a rare high-risk allele ($q = 0.006$) and 3% for non-carriers of the allele. These CSAs highlight characteristics of families useful for linkage studies: families with multiple affected members and early onset of disease are more likely to segregate a single highly penetrant prostate cancer susceptibility gene [Carter et al., 1992; Grönberg et al., 1997a; Schaid et al., 1998].

Linkage Analyses

The first significant prostate cancer linkage analysis published utilized 91 high-risk prostate cancer families from the North America and Sweden [Smith et al., 1996]. This report suggested that a dominantly inherited prostate cancer susceptibility locus (*HPC1*) in the chromosome 1q24-25 region was responsible for 34% of inherited prostate cancer in families studied. Initially, the authors analyzed a set of 66 North American prostate cancer families and observed a lod score of 2.75 with marker D1S218. When an additional 25 North American and Swedish families were added to the analysis, significant evidence for linkage was provided by a lod score of 3.65 at a recombination fraction (θ) = 0.18 with marker D1S2883. The region was refined to an approximate 11-cM stretch between D1S2883 and D1S422. A maximum parametric multipoint lod score of 5.43 was obtained with markers D1S2883, D1S158, and D1S422 under the assumption of heterogeneity ($\alpha = 0.34$) with the postulated locus being close to D1S422 [Smith et al., 1996]. The majority of families evaluated were Caucasian, but it was noted that two African-American families contributed 1.4 to the original lod score. A second report from the same group reported that analysis of 40 North American families in their dataset with an average age at diagnosis <65 years yielded a parametric multipoint lod score of 3.96, whereas for 39 North American families with an older average age at diagnosis, this value was –0.84 [Grönberg et al., 1997c]. When restricted to 14 North American families with average age at diagnosis <60 years, the estimated proportion of families linked was 66%, but decreased to 7% for the families with mean age at diagnosis ≥70 years. A similar age effect was observed in a set of 12 Swedish pedigrees analyzed.

Several groups have sought to confirm prostate cancer linkage to 1q24-25 with

inconsistent results. Cooney et al. [1997] analyzed 20 families with three or more affected men in a nuclear family, two or more men affected at <55 years, or prostate cancer in three successive generations. Analysis of six 1q24-25 markers by multipoint non-parametric linkage (NPL) methods yielded a maximum NPL score of 1.72 (p = 0.045) at marker D1S466. Analysis of six African-American families produced a maximum NPL score of 1.39 (p = 0.08) at D1S158. In another study, Hsieh et al. [1997] reported that non-parametric multipoint linkage analysis of 46 families with mean age of onset <67 years yielded a significant NPL score of 1.83 (p = 0.04) at D1S452.

In contrast, other studies have rejected prostate cancer linkage to 1q24-25. These analyses found two-point lod scores for 1q24-25 markers ranging from –25.11 to –2.49 [McIndoe et al., 1997; Berthon et al., 1998; Eeles et al., 1998]. A lod score of –2.0 is considered significant evidence against linkage. We previously analyzed 49 of the currently reported 150 families for 10 1q24-25 markers spanning 37 cM and found that lod scores for all 10 markers were less than –2.0 at $\theta = 0$ and remained negative at higher θs for most markers [McIndoe et al., 1997]. Eeles et al. [1998] analyzed 136 families with two or more cases of prostate cancer. No significant evidence for linkage was observed at any of six markers studied, including analysis of 35 families with four or more cases. Assuming heterogeneity, it was estimated that 4% of the 136 families were likely to be linked to the *HPC1* region. Finally, Berthon et al. [1998] studied 47 families with a mean of 3.3 affected men per family and observed significantly negative two-point parametric lod scores for three 1q24-25 markers. Subsequently, three other putative prostate cancer loci were mapped: *PCaP* at 1q42.2-43 [Berthon et al., 1998], *HPCX* at Xq27-28 [Xu et al., 1998], and *CAPB* at 1p36 for which evidence is observed in prostate cancer families with a history of primary brain cancer [Gibbs et al., 1999]. Clearly, estimation of the true proportion of high-risk prostate cancer families linked to 1q24-25 will require more detailed analysis in a large number of families, and consideration of families potentially linked at other loci. Here, we evaluate 150 families with three or more affected men for evidence of linkage to the *HPC1* locus using parametric two-point methods, parametric and non-parametric multipoint methods, and sample stratification.

METHODS

Study Subjects

Subject recruitment for the Prostate Cancer Genetic Research Study (PROGRESS) began in July 1995 and is based on the national distribution of a toll-free telephone number encouraging families throughout the country with multiple cases of prostate cancer to call regarding participation in a genetic study. Families of callers are selected if they meet either of the following criteria: 1) three or more first-degree relatives with prostate cancer, 2) prostate cancer in three successive generations, or 3) prostate cancer in two living first-degree relatives diagnosed at <65 years. Since the reporting of cancer diagnosis by second- or third-degree relatives has been shown to be unreliable [Steinberg et al., 1990; Bondy et al., 1994], the pedigrees used in this analysis were reduced so that affected family members who were not sampled (deceased or no contact) and who were more than one generation away from a sampled individual were excluded. Unaffected men aged 45 years or older were coded as

having unknown affected status if they indicated on the questionnaire that they had not had a prostate-specific antigen (PSA) test within the past 5 years, if they did not know if they had had a PSA test, or if they had an elevated or abnormal PSA and did not have physician diagnosed benign prostatic hyperplasia. Samples from 150 families were genotyped at three markers in the 1q24-25 region (D1S1589, D1S518, and D1S1660); samples from a random subset of 139 families were also genotyped at three additional markers within the region (D1S2883, D1S2818, and D1S2127). These six markers are arranged on 1q24-25 as follows: D1S1589—2.84 cM—D1S2883—3.41 cM—D1S2818—2.00 cM—D1S2127—1.89 cM—D1S518—10.25 cM—D1S1660. Markers D1S2883, D1S2818, D1S2127, and D1S518 lie within the region identified by Smith et al. [1996] as likely to contain *HPC1*. Additional information about procedures used for recruitment of families, verification of diagnoses, and collection and genotyping of DNA samples is summarized elsewhere [McIndoe et al., 1997].

Statistical Analysis

The lod score method of parametric two-point linkage analysis used the MLINK component of LINKAGE v.5.1 [Lathrop et al., 1984] and the ANALYZE software package [J. Terwilliger]. HOMOG was used to test for locus heterogeneity and perform two-point analysis assuming heterogeneity [Ott, 1991]. Parametric and non-parametric multipoint analyses used GENEHUNTER v1.2 [Kruglyak et al., 1996]. NPL scores derived from non-parametric multipoint analysis represent a measure of haplotype-sharing among affected individuals. Parametric analyses assumed three models for the autosomal dominant transmission of prostate cancer. Model S1 is described in detail in McIndoe et al. [1997] where it is referred to as the "Seattle" model. Model S1 was used in the analysis of the entire group of 150 families. However, the age-dependent penetrances in Model S1 were replaced by estimates from our data when families were stratified by race and mean age at diagnosis of sampled affected men. Table I shows the genotype-specific penetrances of the varied models used to analyze Caucasian families with mean age at diagnosis ≤65 years (Model S2), Caucasian families with mean age at diagnosis >65 years (Model S3), non-Caucasian families with mean age at diagnosis ≤65 years (Model S4), and non-Caucasian families with mean age at diagnosis >65 years (Model S5). To eliminate the possibility of false-negative findings due to a difference in model specifications, we also used models from other studies that found significant evidence for 1q24-25 linkage. Model A was used in the linkage analysis reported in Smith et al. [1996] and described in reports by McIndoe et al. [1997], where it is referred to as the "Hopkins" model, and Grönberg et al. [1997c]. Model B was used and described by Grönberg et al. [1997c]. Allele frequencies were determined using all individuals in the dataset [Ott, 1992; Terwilliger and Ott, 1994].

The highest power to detect linkage is achieved when homogeneous subsets of data, with respect to etiologic locus, are considered, regardless of the transmission model expected. Grönberg et al. [1997c] observed that groups of families with younger mean ages at diagnosis had higher lod scores than groups of families with older mean ages at diagnosis. Therefore, we stratified families by mean age at diagnosis. We used the mean age at prostate cancer diagnosis of sampled affected men to group families, because the age at diagnosis for those affected men who were able to sub-

TABLE 1. Genotype Specific Penetrances for Models S2, S3, S4, and S5 Used for Caucasian and Non-Caucasian Families Stratified by Mean Age at Diagnosis at Sampled Affected Men

	Mean age of diagnosis							
	Caucasian families				Non-Caucasian families			
	≤65 years (Model S2)		>65 years (Model S3)		≤65 years (Model S4)		>65 years (Model S5)	
Liability class	pp[a]	Pp/PP	pp[a]	Pp/PP	pp[a]	Pp/PP	pp[a]	Pp/PP
1: All women, men aged ≤29 years	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2: Men aged 30–39 years	0.001	0.004	0.001	0.000	0.001	0.003	0.001	0.000
3: Men aged 40–49 years	0.001	0.051	0.001	0.004	0.001	0.046	0.001	0.004
4: Men aged 50–59 years	0.005	0.286	0.005	0.054	0.005	0.288	0.005	0.053
5: Men aged 60–69 years	0.010	0.764	0.010	0.430	0.010	0.765	0.010	0.429
6: Men aged 70–79 years	0.050	0.880	0.050	0.880	0.050	0.880	0.050	0.880
7: Men aged 80 years +	0.050	0.880	0.050	0.880	0.050	0.880	0.050	0.880

[a]Allele P is disease allele with frequency = 0.003.

mit questionnaires and be sampled was expected to be more reliable than the age at diagnosis of all affected men. To further increase homogeneity, we also stratified families by race, number of affected individuals, and whether prostate cancer occurred in two or more generations. We also conducted the analyses including only families who had lod scores <0.35 at any θ at markers in the *PCaP* region (D1S2785), *HPCX* region (DXS984, DXS1200, and DXS1193), or *CAPB* region (D1S407). We used the computer program SIMLINK [Boehnke, 1986] to assess the power of this group of 150 families to detect two-point linkage to a marker with polymorphism information content of 0.84 using lod methods, assuming 88% penetrance for carriers of the disease gene and 5% penetrance for non-carriers by age 85 years.

RESULTS

The 150 families in this report included 2,176 individuals with 640 affected men having an average age of prostate cancer diagnosis of 66.8 years (range, 39–94) (Table II). The families had an average of 4.3 affected men (range, 3–10) per family, and the mean age at diagnosis per family was 66.7 years (range, 52.8–78.0). These characteristics of the overall dataset were similar to the 49 families previously analyzed [McIndoe et al., 1997]. Sixty-six Caucasian families, two African-American families, and two Native-American families had mean age of diagnosis of sampled affected men ≤65 years. Seventy-eight Caucasian families, a Japanese family, and a Latino family had mean age at diagnosis of sampled affected men >65 years.

Sampled affected men were diagnosed with prostate cancer between the years of 1974 and 1997. For 491 (94.4%) of 520 sampled affected men, medical records were received, and all but one of the medical records confirmed the prostate cancer diagnosis. A total of 1,128 individuals, including 511 affected men, were genotyped for at least one 1q24-25 marker. There was an average of 3.4 genotyped affected men (range, 2–7) per family, and the mean age of diagnosis for genotyped affected men per family was 65.9 years (range, 50.8–78.0). Fifty-two unaffected men aged ≥45 years were coded as unknown affected status because they did not report a recent normal PSA test (see methods).

Analysis of All Families

Two-point lod scores at D1S1589, D1S2883, D1S2818, D1S2127, D1S518, and D1S1660 for all families analyzed with Models S1, A, and B are presented in Table III. While 150 families were analyzed at D1S1589, D1S518, and D1S1660, 139 were analyzed at D1S2883, D1S2818, and D1S2127. With all three models, there was significant evidence against linkage to each 1q24-25 marker. The lod scores at small θs were consistently below the –2.0 cutoff for evidence against linkage. Lod scores became positive at higher θs for D1S2883 (lod = 0.02, θ = 0.42), D1S2127 (lod = 0.09, θ = 0.38), and D1S1660 (lod = 0.16, θ = 0.34), using model S1, but remained negative at other markers. Assuming heterogeneity, analysis using HOMOG showed that two-point lod scores increased to 0.03 (θ = 0) with α = 0.04 at D1S2883 and 0.17 (θ = 0) with α = 0.09 at D1S2127 and estimated that α = 0 for the markers. When the 49 families previously analyzed [McIndoe et al., 1997] were removed from the analysis, the two-point lod scores at θ = 0 were less than –9.40 for all six

TABLE II. Characteristics of 150 Prostate Cancer Families and Subsets Based on Race and Mean Age at Diagnosis of Sampled Affected Men

		Mean age of diagnosis			
		Caucasian families		Non-Caucasian families	
	Total group	≤65 years	>65 years	≤65 years	>65 years
Number of families	150	66	78	4	2
Number of individuals	2,176	922	1,135	96	23
Number of affected men	640	275	330	27	8
Number of genotyped affected men*	511	219	264	21	7
Mean age at diagnosis, years (range)	66.8 (39–94)	63.3 (39–87)	69.8 (40–93)	63.9 (53–80)	72.1 (60–94)
Mean age of diagnosis for genotyped affected mean, years (range)*	65.9 (40–87)	62.0 (40–82)	69.3 (47–87)	63.2 (53–80)	69.0 (60–74)
Mean number of affected men per family (range)	4.3 (3–10)	4.2 (3–9)	4.2 (3–8)	6.8 (4–10)	4.0 (3–5)
Mean age at diagnosis of affected men per family, years (range)	66.7 (52.8–78.0)	63.0 (52.8–70.7)	69.9 (63.4–78.0)	62.9 (59.5–65.0)	72.0(71.7–72.4)
Mean number of genotyped affected men per family (range)*	3.4 (2–7)	3.3 (2–5)	3.4 (2–5)	5.3 (3–8)	3.5 (3–4)
Mean age at diagnosis of genotyped affected men per family, years (range)*	65.9 (50.8–78.0)	62.0 (50.8–66.0)	69.4 (65.0–78.0)	62.4 (57.5–64.8)	69.3 (67.0–71.7)

*Genotyped affected mean are defined as affected men who werre genotyped for at least one marker in the 1q24-25 region.

TABLE III. Two-Point Lod Scores for Prostate Cancer Families Analyzed with Models S1, A, and B

Marker (distance, cM)	Number of families	Model	Recombination fraction, θ: 0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
D1S1589 (—)	150	S1	−26.26	−20.60	−13.31	−8.71	−2.76	−0.61	−0.06	0
		A	−67.01	−40.46	−22.91	−14.28	−4.40	−1.04	−0.12	0
		B	−8.64	−7.18	−4.99	−3.44	−1.21	−0.32	−0.04	0
D1S2883 (2.84)	139	S1	−21.43	−16.41	−10.19	−6.44	−1.81	−0.27	−0.02	0
		A	−52.86	−31.46	−19.29	−10.43	−2.89	−0.53	−0.02	0
		B	−6.69	−5.58	−3.90	−2.70	−0.96	−0.25	−0.02	0
D1S2818 (3.41)	139	S1	−18.42	−14.22	−9.06	−5.92	−1.90	−0.44	−0.05	0
		A	−47.73	−28.08	−15.44	−9.52	−2.95	−0.73	−0.10	0
		B	−4.93	−4.09	−2.81	−1.91	−0.62	−0.13	−0.01	0
D1S2127 (2.00)	139	S1	−18.81	−14.16	−8.74	−5.49	−1.42	−0.09	0.08	0
		A	−43.78	−26.17	−14.32	−8.63	−2.33	−0.35	0.03	0
		B	−4.80	−3.78	−2.38	−1.44	−0.21	0.13	0.09	0
D1S518 (1.89)	150	S1	−30.83	−24.11	−15.48	−10.07	−3.15	−0.69	−0.07	0
		A	−84.01	−50.47	−28.48	−17.71	−5.44	−1.28	−0.15	0
		B	−12.15	−9.95	−6.84	−4.71	−1.71	−0.48	−0.08	0
D1S1660 (10.25)	150	S1	−23.26	−17.19	−9.98	−5.82	−1.11	0.09	0.11	0
		A	−70.92	−40.53	−21.13	−12.25	−3.02	−0.42	0.02	0
		B	−4.89	−3.80	−2.22	−1.20	−0.02	0.19	0.09	0

markers, using model S1, and they showed a similar pattern at higher θs as the total dataset. Power computations estimated an expected lod score of 0.46 at $\theta = 0$ for the 150 families if 34% of families were linked to *HPC1*. Thus, although the power to achieve a lod score of 3.0 is very low, the lod score range of −30.83 to −18.42 is incompatible with linkage of 34% of the sample and provides strong evidence against linkage for this sample. In fact, SIMLINK results indicate that if only 10% of the families were linked, we would expect positive lod scores at $\theta = 0$.

The families were also analyzed with more specific versions of Model S1 (Table I). When summed, there was again evidence against linkage at all six markers with two-point lod scores less than −27.90 at $\theta = 0$ (data not shown). At higher θs, lod scores became positive for markers D1S2883, D1S2127, and D1S1660, but remained negative for other markers. Figure 1 displays the distribution of two-point lod scores using these models at marker D1S518, which lies within the proposed *HPC1* region. Two-point lod scores at this marker ranged from −2.05 to 0.66, and the median lod score was −0.12. While the majority of families have negative lod scores, we note that there are 21 families with lod scores >0.30.

Multipoint lod score analysis was performed on the total group of families on six markers (D1S1589, D1S2883, D1S2818, D1S2127, D1S518, and D1S1660), and results are given in Table IV. Eleven families were not genotyped at markers D1S2883, D1S2818, and D1S2127. Using Model S1, parametric multipoint lod scores throughout the region ranged from −43.25 to −29.00 at positions corresponding to markers. Assuming heterogeneity, a maximum HLOD of 0.023 with an α of 0.026 was found at a position corresponding to marker D1S2127; positive HLODs were also seen at D1S2818 and D1S1660. Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

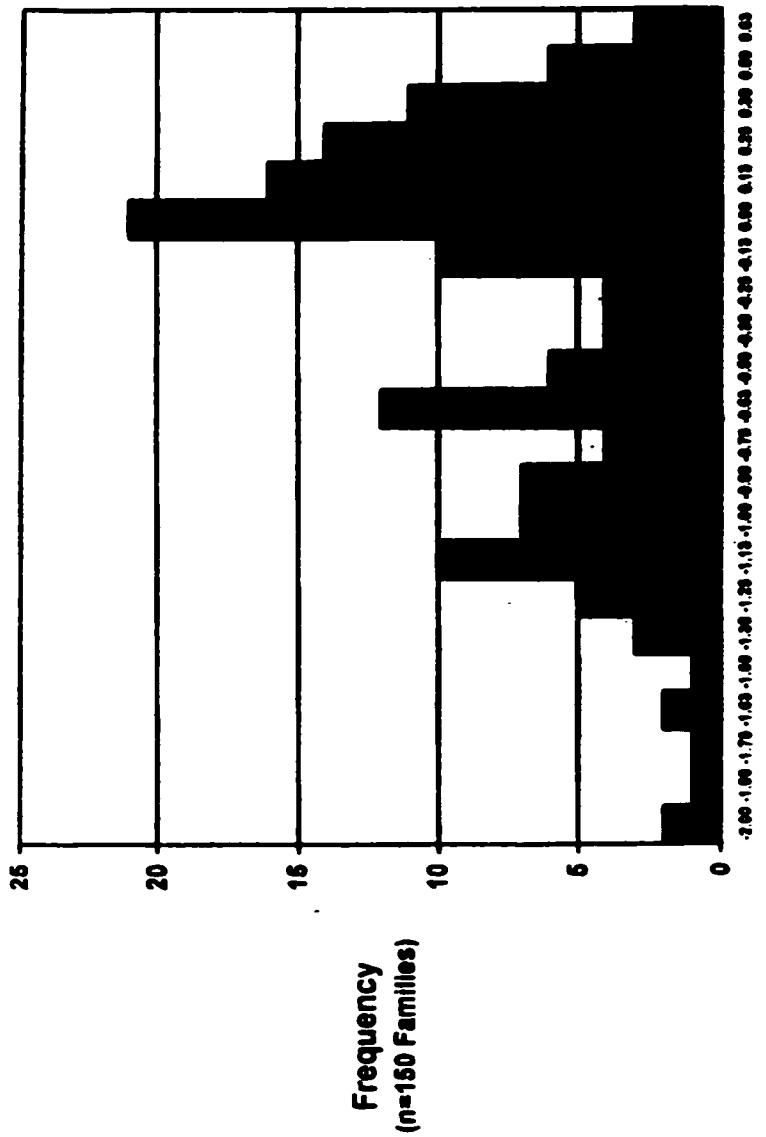

Fig. 1. Lod scores at D1S518 for 150 prostate cancer families using Models S2, S3, S4, and S5. Lod scores plotted represent lod scores with the largest absolute value at any θ.

TABLE IV. Multipoint Lod Scores for 150 Prostate Cancer Families[a]

		Parametric			Non-parametric	
Marker	Distance (cM)	Lod	HLOD	α	HPL score	*P*-Value
D1S1589	—	−39.87	−0.003	0.001	−0.65	0.74
D1S2883	2.84	−40.28	−0.004	0.009	−0.19	0.57
D1S2818	3.41	−39.54	0.017	0.026	0.15	0.43
D1S2127	2.00	−41.53	0.023	0.026	0.21	0.41
D1S518	1.89	−43.25	−0.002	0.0004	−0.19	0.57
D1S1660	10.25	−29.00	0.006	0.025	0.49	0.31

[a]Parametric lod scores, HLOD scores, and α were calculated using Model S1. Eleven families were not genotyped at markers D1S2883, D1S2818, and D1S2127.

Analysis of Family Subsets Based on Ethnicity, Mean Age of Diagnosis, and Number of Affected Men

The dataset was further restricted to Caucasian families and stratified by mean age at diagnosis of sampled affected men and number of affected men (≤65 years, ≤60 years, >65 years, ≤65 years with five or more affected men, ≤65 years with prostate cancer in at least two generations). Parametric analyses of these groups of families used Models S2 and S3. Tables V, VI, and VII describe two-point results for markers D1S1589, D1S518, and D1S1660, respectively, for subgroups of families. In each subgroup at all six 1q24-25 markers, linkage was rejected and lod scores remained negative at higher θs, except in a few groups of families at certain markers. Table VIII shows results of multipoint analysis on subsets of families. Parametric multipoint analysis consistently yielded lod scores of less than −7.45 at positions corresponding to markers. Non-parametric multipoint linkage produced non-significant NPL scores throughout the region in these subgroups.

Analysis of 78 Caucasian families with mean age at diagnosis >65 years (four of these families were not genotyped at D1S2883, D1S2818, and D1S2127) produced two-point lod scores less than −8.69 at $\theta = 0$. Positive lod scores were observed at higher θs with the following maximum lod scores: D1S1589, lod = 0.11, $\theta = 0.36$; D1S2883, lod = 0.45, $\theta = 0.28$; D1S2818, lod = 0.05, $\theta = 0.36$; D1S2127, lod = 0.49, $\theta = 0.28$; D1S518, lod = 0.27, $\theta = 0.32$; and D1S1660, lod = 0.07, $\theta = 0.36$. Assuming heterogeneity within this group, two-point lod scores rose to 0.59 ($\alpha = 0.20$, $\theta = 0$) at D1S2127 and 0.30 ($\alpha = 0.17$, $\theta = 0$) at D1S518. Multipoint results revealed lod scores of less than −15.68 at positions corresponding to markers; however, analyses assuming heterogeneity produced positive HLODs at all markers except D1S1660. A maximum HLOD was observed at marker D1S2127 of 0.370 with an α of 0.123. No NPL scores were significant in this subgroup; however, an NPL score of 1.68 at D1S2127 reached marginal significance ($p = 0.051$), with *p*-values of 0.10 and 0.11 at surrounding markers. This marginally significant NPL score at D1S2127 is not consistent with parametric multipoint results. This discrepancy may be explained by 1) the small NPL *p*-value may be the result of chance due to multiple comparisons; 2) the model used in parametric analyses may be inappropriate; or 3) men who do not have the disease share a haplotype with affected men in these families. Examination of haplotypes of the nine families with negative multipoint lod scores and positive NPL scores indicate that the latter possibility is likely.

TABLE V. Two-Point Lod Scores for Stratified Subsets of Caucasian Prostate Cancer Families at Marker D1S1589

Mean age at diagnosis	Number of families	Affected men	Recombination fraction 0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	66	—	−21.45	−15.64	−9.77	−6.49	−2.37	−0.74	−0.14	0
≤60	20	—	−5.84	−4.13	−2.52	−1.67	−0.62	−0.21	−0.04	0
>65[a]	78	—	−13.23	−9.97	−5.99	−3.61	−0.75	0.05	0.08	0
≤65	21	≥5	−6.55	−4.91	−3.10	−2.02	−0.65	−0.15	−0.02	0
≤65	43	in >1 generation	−10.42	−7.50	−4.60	−3.00	−1.03	−0.29	−0.06	0

[a]All family groups were analyzed using Model S2, except this group, which was analyzed with Model S3.

TABLE VI. Two-Point Lod Scores for Stratified Subsets of Caucasian Prostate Cancer Families at Marker D1S518

Mean age at diagnosis	Number of families	Affected men	Recombination fraction							
			0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	66	—	−34.50	−24.55	−15.23	−10.16	−3.88	−1.32	−0.29	0
≤60	20	—	−11.77	−8.70	−5.69	−3.99	−1.74	−0.67	−0.16	0
>65[a]	78	—	−12.49	−9.36	−5.44	−3.09	−0.36	0.26	0.14	0
≤65	21	≥5	−16.60	−11.56	−7.17	−4.82	−1.89	−0.66	−0.15	0
≤65	43	in >1 generation	−25.59	−18.06	−11.36	−7.73	−3.15	−1.16	−0.27	0

[a]All family groups were analyzed using Model S2, except this group, which was analyzed with Model S3.

TABLE VII. Two-Point Lod Scores for Stratified Subsets of Caucasian Prostate Cancer Families at Marker D1S1660

Mean age at diagnosis	Number of families	Affected men	Recombination fraction							
			0.00	0.02	0.06	0.10	0.20	0.30	0.40	0.50
≤65	66	—	−18.92	−13.07	−7.56	−4.69	−1.41	−0.32	−0.03	0
≤60	20	—	−7.11	−5.15	−3.21	−2.14	−0.80	−0.25	−0.05	0
>65[a]	78	—	−16.09	−11.82	−6.89	−4.09	−0.88	−0.01	0.06	0
≤65	21	≥5	−7.04	−4.75	−2.71	−1.69	−0.54	−0.15	−0.03	0
≤65	43	in >1 generation	−14.36	−9.73	−5.50	−3.35	−0.95	−0.20	−0.01	0

[a]All family groups were analyzed using Model S2, except this group, which was analyzed with Model S3.

TABLE VIII. Multipoint Lod Scores for Stratified Subsets of Caucasian Prostate Cancer Families

Family group			Marker	Parametric			Non-parametric	
Mean age at diagnosis	Number of families	Affected men	(distance, cM)	Lod	HLOD	α	NPL score	*P*-value
≤65	66	—	D1S1589 (—)	-31.22	-0.001	0.0001	-1.49	0.94
			D1S2883 (2.84)	-34.87	-0.001	0.0002	-1.79	0.97
			D1S2818 (3.41)	-38.01	-0.0004	0.0001	-1.45	0.93
			D1S2127 (2.00)	-41.20	-0.0002	0.0000	-1.90	0.98
			D1S518 (1.89)	-42.74	-0.0002	0.0000	-1.67	0.96
			D1S1660 (10.25)	-29.54	-0.001	0.0001	-0.78	0.78
≤60*	20	—	D1S1589 (—)	-9.13	-0.0003	0.0001	-1.21	0.89
			D1S2883 (2.84)	-11.79	-0.0003	0.0001	-1.60	0.95
			D1S2818 (3.41)	-12.92	-0.0002	0.0000	-1.43	0.93
			D1S2127 (2.00)	-12.11	-0.0002	0.0000	-1.35	0.92
			D1S518 (1.89)	-13.40	-0.0001	0.0000	-1.57	0.95
			D1S1660 (10.25)	-9.77	-0.0001	0.0000	-0.90	0.81
>65	78	—	D1S1589 (—)	-15.68	0.084	0.080	0.59	0.27
			D1S2883 (2.84)	-16.46	0.146	0.094	1.30	0.10
			D1S2818 (3.41)	-18.86	0.166	0.085	1.28	0.10
			D1S2127 (2.00)	-17.69	0.370	0.123	1.68	0.051
			D1S518 (1.89)	-17.56	0.023	0.044	1.22	0.11
			D1S1660 (10.25)	-17.85	-0.0001	0.022	0.78	0.22
≤65	21	≥5 in >1 generation	D1S1589 (—)	-7.45	0.012	0.051	0.12	0.42
			D1S2883 (2.84)	-8.00	0.093	0.111	0.41	0.32
			D1S2818 (3.41)	-8.36	-0.001	0.002	-0.05	0.49
			D1S2127 (2.00)	-10.93	-0.0002	0.0001	-0.16	0.53
			D1S518 (1.89)	-13.23	-0.0002	0.0000	-0.58	0.70
			D1S1660 (10.25)	-7.98	-0.001	0.003	-0.14	0.52
≤65	43		D1S1589 (—)	-29.36	-0.002	0.001	-0.27	0.60
			D1S2883 (2.84)	-34.50	-0.003	0.004	-0.47	0.67
			D1S2818 (3.41)	-35.51	0.031	0.032	0.09	0.45
			D1S2127 (2.00)	-38.27	0.020	0.024	0.12	0.44
			D1S518 (1.89)	-36.95	-0.001	0.001	-0.06	0.51
			D1S1660 (10.25)	-29.06	-0.002	0.001	-0.05	0.51

*Parametric lod scores, HLOD scores, and α were calculated using Model S2, except this group, which was analyzed with Model S3.

Analysis of 66 Caucasian families with a mean age at diagnosis of ≤65 years revealed no evidence for linkage with consistently negative two-point and multipoint lod scores (even assuming heterogeneity) and non-significant NPL scores (Tables V–VIII). Restricting to 20 Caucasian families with a mean age of diagnosis of ≤60 years (one family was not genotyped at D1S2883, D1S2818, and D1S2127) revealed two-point lod scores less than –2.00 at $\theta = 0$ that remained negative a higher θs for all markers except D1S2127. At $\theta = 0$, the two-point lod score at D1S2127 was –1.03, and assuming heterogeneity, this lod score rose to 0.05 ($\alpha = 0.19$, $\theta = 0$). Multipoint analysis, however, revealed negative lod scores and HLODs and estimates of $\alpha = 0$ (Table VIII).

Caucasian families with young age at diagnosis were further stratified by number of affected men per family. Analysis of 21 families with a mean age at diagnosis of ≤65 years and five or more affected men (two families were not genotyped at D1S2883, D1S2818, and D1S2127) revealed no evidence for linkage (Tables V–VIII). Assuming heterogeneity, however, a two-point lod score of 0.07 ($\alpha = 0.13$, $\theta = 0$) is obtained at DS2883 and a lod score of 0.02 ($\alpha = 0.56$, $\theta = 0.32$) is obtained at DS2818. Multipoint analysis revealed a maximum HLOD of 0.093 with an α of 0.111 at marker D1S2883 and a lod score of 0.02 ($\alpha = 0.56$, $\theta = 0.32$) is obtained at DS2818. Multipoint analysis revealed a maximum HLOD of 0.093 with an α of 0.111 at marker D1S2883. Analysis of 43 families with mean age at diagnosis of ≤65 years and prostate cancer in more than one generation (seven families were not genotyped at D1S2883, D1S2818, and D1S2127) also revealed no evidence for linkage. In this group, however, a two-point lod score of 0.49 ($\alpha = 0.21$, $\theta = 0$) is obtained at DS2127 if heterogeneity is assumed. Multipoint analysis revealed a maximum HLOD of 0.031 ($\alpha = 0.032$) at a position corresponding to marker D1S2818 in this group.

We analyzed six non-Caucasian families at 1q24-25 markers. Three of these families had positive two-point lod scores, including one African-American family with a lod score of 0.34 at marker D1S518 ($\theta = 0$) and positive lod scores at all other markers. Three of the non-Caucasian families had negative two-point lod scores at all markers, including a second African-American family.

Analysis of Family Subsets Based on Potential Linkage to Other Loci

In an effort to decrease heterogeneity due to linkage at other loci, 87 families were also genotyped at marker D1S2785 in the *PCaP* region, at markers DXS984, DXS1200, and DXS1193 in the *HPCX* region, and at marker D1S407 in the *CAPB* region. Although a small positive lod score is not conclusive evidence of linkage in a given family, we excluded 41 families from the *HPC1* analysis that had a lod score >0.35 at any θ for these markers and 63 families that were not genotyped at all of these markers to exclude families that might possibly be linked to these other loci. Forty-one of these excluded families also had a positive lod score at D1S518, and the median lod score at D1S518 ($\theta = 0$) for excluded families was –0.06 (range, –1.22 to 0.67).

In 46 families without evidence of linkage to *PCaP*, *HPCX*, or *CAPB* (including one non-Caucasian family and three families not genotyped at D1S2883, D1S2818, and D1S2127), there was no evidence for linkage using Models S1, A, and B (Table IX). Using Model S1, two-point lod scores were < –2.0 at $\theta = 0$ remained negative at higher values of θ for markers D1S518 and D1S2883, but became slightly positive

TABLE IX. Parametric Two-Point and Multipoint Lod Scores for 46 Prostate Cancer Families Without Evidence of Linkage to Other Loci[a]

		Two-point						Multipoint		
				Assuming heterogeneity						
Model	Marker (distance, cM)	Lod, $\theta = 0$	Maximum lod	θ	Maximum lod	θ	α	Lod	HLOD	α
S1	D1S1589 (—)	−5.02	0.10	0.32	0.10	0.32	0.06	−7.56	0.325	0.163
	D1S2883 (2.84)	−6.33	0.00	0.50	0.00	0.50	0.00	−7.24	0.429	0.181
	D1S2818 (3.41)	−3.35	0.17	0.28	0.17	0.28	0.00	−6.84	0.505	0.198
	D1S2127 (2.00)	−2.89	0.40	0.24	0.40	0.24	0.00	−8.88	0.113	0.099
	D1S518 (1.89)	−10.55	0.00	0.50	0.00	0.50	0.00	−12.00	−0.001	0.0003
	D1S1660 (10.25)	−8.17	0.01	0.42	0.01	0.42	0.00	−10.65	−0.001	0.001
A	D1S1589 (—)	−16.29	0.06	0.36	0.06	0.36	0.00	−22.39	0.017	0.038
	D1S2883 (2.84)	−21.89	0.00	0.50	0.00	0.50	0.00	−27.78	0.021	0.038
	D1S2818 (3.41)	−17.23	0.04	0.36	0.04	0.36	0.03	−30.11	0.027	0.040
	D1S2127 (2.00)	−11.96	0.24	0.28	0.24	0.28	0.00	−30.76	−0.003	0.006
	D1S518 (1.89)	−30.25	0.00	0.50	0.00	0.46	0.32	−33.76	−0.001	0.0001
	D1S1660 (10.25)	−22.97	0.00	0.50	0.00	0.50	0.00	−29.71	−0.0004	0.0001
B	D1S1589 (—)	−1.80	0.05	0.30	0.05	0.30	0.00	−2.74	0.071	0.139
	D1S2883 (2.84)	−2.50	0.00	0.50	0.00	0.50	0.00	−2.70	0.040	0.125
	D1S2818 (3.41)	−1.01	0.10	0.26	0.10	0.26	0.00	−3.36	−0.003	0.046
	D1S2127 (2.00)	−0.76	0.27	0.20	0.27	0.20	0.00	−4.42	−0.002	0.001
	D1S518 (1.89)	−6.05	0.00	0.50	0.00	0.50	0.00	−6.03	−0.001	0.0002
	D1S1660 (10.25)	−2.69	0.00	0.42	0.00	0.42	0.00	−4.20	−0.001	0.001

[a]Nonparametric multipoint analysis produced non-significant NPL scores throughout the region.

for markers D1S1589 and D1S1660. At marker D1S2127, lod scores peaked to 0.40 at $\theta = 0.24$, and at D1S2818 they reached 0.17 at $\theta = 0.28$. When heterogeneity was assumed, a maximum two-point lod score of 0.10 was observed at D1S1589 ($\theta = 0.32$, $\alpha = 0.06$). Multipoint analysis revealed no evidence for linkage. Using Model S1, parametric multipoint lod scores were less than –6.83 at positions corresponding to markers. Assuming heterogeneity, a maximum HLOD of 0.506 with an α of 0.198 was found at a position corresponding to marker D1S2818. Positive HLODs were also seen at markers D1S1589 (HLOD = 0.325, $\alpha = 0.163$), D1S2883 (HLOD = 0.429, $\alpha = 0.181$), and D1S2127 (HLOD = 0.113, $\alpha = 0.099$). Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

Caucasian families without evidence for linkage to other loci were stratified based on mean age at diagnosis of sampled affected men. Two-point analysis of 24 Caucasian families with mean age at diagnosis ≤65 years (two families were not genotyped at D1S2883, D1S2818, and D1S2127) yielded lod scores less than –3.56 at $\theta = 0$ for all markers, using model S2 (Table X). Two-point lod scores reached 0.31 at D1S2818 ($\theta = 0.24$), became slightly positive at D1S1589 (lod = 0.02, $\theta = 0.34$) and D1S2127 (lod = 0.03, $\theta = 0.34$), and remained negative at higher θs for other markers. When heterogeneity was assumed, HOMOG revealed a lod score of 0.02 at $\theta = 0.32$ with $\alpha = 0.29$ at D1S1589. Parametric multipoint analysis consistently yielded negative lod scores at positions corresponding to markers. Assuming heterogeneity, however, a maximum HLOD of 0.003 with $\alpha = 0.027$ at a position corresponding to marker D1S2127 in this group. In this group, HLODs at other markers were negative and all NPL scores were non-significant.

Analysis of nine Caucasian families without evidence of linkage to *PCaP, HPCX*, or *CAPB* and with a mean age at diagnosis of ≤60 years (one family was not genotyped at D1S2883, D1S2818, and D1S2127) produced significantly negative two-point lod scores (Table X), except at marker D1S2127 (lod = 0.31, $\theta = 0$). When limited to eight families in this group that were genotyped at all six 1q24-25 markers, the two-point lod scores at $\theta = 0$ for all six markers were –1.38 at D1S1589, –4.45 at D1S2883, –3.20 at D1S2818, 0.31 at D1S2127, –4.55 at D1S518, and –2.20 at D1S1660. The positive lod score at marker D1S2127 peaked at $\theta = 0$; four families contributed positive and four families contributed negative lod scores. Assuming heterogeneity, the lod score at marker D1S2127 reached 0.32 ($\theta = 0$) with $\alpha = 0.07$. Multipoint analysis, however, revealed negative parametric lod scores at all markers (even assuming heterogeneity) and non-significant NPL scores.

Twenty-one Caucasian families with a mean age at diagnosis of >65 years and without evidence of linkage to other loci were genotyped at all six 1q24-25 markers. Two-point analysis using Model S3 yielded negative two-point lod scores at $\theta = 0$ (Table X). Lod scores at D1S1589 and D1S2127 were not less than –2.0 at $\theta = 0$ in this group. Lod scores became positive at higher at θs at D1S1589 (lod = 0.06, $\theta = 0.34$), D1S2883 (lod = 0.03, $\theta = 0.36$), and D1S2127 (lod = 0.35, $\theta = 0.22$). No evidence for heterogeneity was detected in two-point analysis ($\alpha = 0$ at all markers). Multipoint analysis assuming heterogeneity, however, revealed evidence for heterogeneity at positions corresponding to markers D1S1589 (HLOD = 0.041, $\alpha = 0.117$) and D1S2883 (HLOD = 0.026, $\alpha = 0.092$). Nonetheless, parametric multipoint lod scores were less than –2.97 at all markers and NPL scores were non-significant.

TABLE X. Two-Point and Multipoint Lod Scores for Subgroups of Caucasian Prostate Cancer Families Without Evidence of Linkage to Other Loci

		Two-point						Multipoint				
					Assuming heterogeneity			Parametric			Non-parametric	
Family group	Marker (distance, cM)	Lod, $\theta = 0$	Maximum lod	θ	Maximum lod	θ	α	Lod	HLOD	α	NPL score	*P*-value
24 families, mean age at diagnosis ≤65 years	D1S1589 (—)	−5.62	0.02	0.34	0.02	0.32	0.29	−8.81	−0.002	0.003	−0.65	0.74
	D1S2883 (2.84)	−6.62	0.00	0.50	0.00	0.50	0.00	−9.06	−0.002	0.011	−0.79	0.78
	D1S2818 (3.41)	−3.56	0.31	0.24	0.31	0.24	0.00	−9.74	0.003	0.027	−0.25	0.58
	D1S2127 (2.00)	−4.59	0.03	0.36	0.03	0.36	0.00	−12.63	−0.001	0.001	−0.78	0.78
	D1S518 (1.89)	−13.91	0.00	0.50	0.00	0.50	0.00	−14.35	−0.0004	0.0002	−0.85	0.80
	D1S1660 (10.25)	−7.06	0.00	0.44	0.00	0.44	0.00	−10.82	−0.001	0.0003	−0.28	0.59
9 families mean age at diagnosis ≤60 years	D1S1589 (—)	−2.57	0.00	0.50	0.00	0.50	0.00	−3.46	−0.001	0.004	−0.66	0.74
	D1S2883 (2.84)	−4.45	0.00	0.50	0.00	0.50	0.00	−4.37	−0.001	0.002	−1.00	0.84
	D1S2818 (3.41)	−3.20	0.00	0.50	0.00	0.50	0.00	−4.43	−0.001	0.001	−0.44	0.66
	D1S2127 (2.00)	0.31	0.31	0.00	0.31	0.00	0.07	−4.29	−0.001	0.001	−0.43	0.65
	D1S518 (1.89)	−5.94	0.00	0.50	0.00	0.50	0.00	−5.62	−0.0001	0.0001	−0.70	0.75
	D1S1660 (10.25)	−3.32	0.00	0.50	0.00	0.50	0.00	−3.78	−0.0002	0.0001	−0.09	0.52
21 families, mean age at diagnosis >65 years	D1S1589 (—)	−1.99	0.06	0.34	0.06	0.34	0.00	−2.98	0.041	0.117	0.62	0.26
	D12883 (2.84)	−2.69	0.03	0.36	0.03	0.36	0.00	−3.65	0.026	0.092	0.70	0.24
	D1S2818 (3.41)	−2.96	0.00	0.50	0.00	0.50	0.00	−5.16	−0.001	0.001	0.39	0.34
	D1S2127 (2.00)	−1.65	0.35	0.22	0.35	0.22	0.00	−5.09	−0.001	0.001	0.45	0.32
	D1S518 (1.89)	−2.85	0.00	0.50	0.00	0.50	0.00	−4.95	−0.0003	0.0002	0.10	0.44
	D1S1660 (10.25)	−4.54	0.00	0.42	0.00	0.42	0.00	−5.26	−0.001	0.002	−0.06	0.51
8 families mean age at 65 years, ≥5 affected men per family	D1S1589 (—)	−1.94	0.10	0.26	0.10	0.26	0.00	−3.78	−0.0002	0.0001	−0.05	0.66
	D1S2883 (2.84)	−1.27	0.03	0.32	0.03	0.32	0.00	−3.72	−0.0001	0.0001	−0.66	0.71
	D1S2818 (3.41)	−0.09	0.40	0.12	0.40	0.12	0.00	−5.25	−0.0000	0.0000	−0.77	0.77
	D1S2127 (2.00)	−2.30	0.07	0.30	0.07	0.30	0.00	−5.63	−0.0000	0.0000	−0.90	0.82
	D1S518 (1.89)	−6.22	0.00	0.50	0.00	0.50	0.00	−6.91	−0.0000	0.0000	−1.01	0.85
	D1S1660 (10.25)	−3.63	0.00	0.50	0.00	0.50	0.00	−5.66	−0.0000	0.0000	−0.91	0.82

(continued)

TABLE X. Two-Point and Multipoint Lod Scores for Subgroups of Caucasian Prostate Cancer Families Without Evidence of Linkage to Other Loci (*continued*)

		Two-point						Multipoint				
					Assuming heterogeneity			Parametric			Non-parametric	
Family group	Marker (distance, cM)	Lod, $\theta = 0$	Maximum lod	θ	Maximum lod	θ	α	Lod	HLOD	α	NPL score	*P*-value
19 families,	D1S1589 (—)	−4.37	0.00	0.50	0.00	0.50	0.00	−5.38	0.120	0.130	0.01	0.48
mean age at	D1S2883 (2.84)	−3.94	0.04	0.32	0.04	0.32	0.00	−6.09	0.190	0.147	−0.08	0.51
diagnosis	D1S2818 (3.41)	−2.97	0.01	0.36	0.01	0.36	0.00	−7.77	0.074	0.090	−0.03	0.49
≤65 years,	D1S2127 (2.00)	−3.48	0.13	0.24	0.13	0.24	0.00	−8.26	0.039	0.069	−0.11	0.53
prostate	D1S518 (1.89)	−10.61	0.00	0.50	0.00	0.50	0.00	−10.82	−0.001	0.001	−0.43	0.65
cancer in >1	D1S1660 (10.25)	−5.57	0.04	0.32	0.04	0.32	0.00	−7.60	−0.001	0.001	0.14	0.43
generation												

[a]Parametric lod scores, HLOD scores, and α were calculated uisng Model S2, except this group, which was analyzed using Model S3.

Analyses were also performed on groups of Caucasian families without evidence of linkage to other loci based on number of affected men per family. In a group of eight Caucasian families with mean age at diagnosis for sampled affected men ≤65 years and five or more affected men years (one family was not genotyped at D1S2883, D1S2818, and D1S2127), linkage could not be rejected D1S1589, D1S2883, or D1S2818, using two-point analysis (Table X). Lod scores became positive at higher θs at markers D1S1589 (lod = 0.10 at θ = 0.26), D1S2883 (lod = 0.03 at θ = 0.32), [D1S2818 (lod = 0.40 at θ = 0.2)], and [D1S2127 (lod = 0.07 at θ = 0.3)]. It is likely that this group of families has limited power to detect or reject linkage because of its small number of families. Analysis using HOMOG detected no evidence for heterogeneity. Multipoint analysis revealed negative parametric lod scores at all markers (even assuming heterogeneity) and non-significant NPL scores.

Nineteen Caucasian families without evidence of linkage to *PCaP, HPCX,* or *CAPB*, with mean age at diagnosis ≤65 years, and with prostate cancer in more than one generation (one family was not genotyped at D1S2883, D1S2818, and D1S2127) yielded two-point lod scores of less than −2.0 at θ = 0 for all markers (Table X). Lod scores remained negative at higher θs for D1S1589 and D1S518, but became positive at the other markers. Analysis using HOMOG detected no evidence for heterogeneity using two-point analysis. Multipoint analysis revealed parametric lod scores less than −5.38 at all six markers; however, assuming heterogeneity, positive HLODs and evidence for heterogeneity were observed at markers D1S1589 (HLOD = 0.120, α = 0.130), D1S2883 HLOD = 0.190, α = 0.147), D1S2818 (HLOD = 0.074, α = 0.090), and D1S2127 (HLOD = 0.039, α = 0.069). Non-parametric multipoint linkage produced non-significant NPL scores throughout the region.

DISCUSSION

The original finding of *HPC1* linkage on chromosome 1q24-25 [Smith et al., 1996] has proven challenging to replicate. Some reports supported prostate cancer linkage to this region [Cooney et al., 1997; Grönberg et al., 1997c; Hsieh et al., 1997], while others did not [McIndoe et al., 1997; Berthon et al., 1998; Eeles et al., 1998]. No significant evidence for linkage of a prostate cancer susceptibility locus to 1q24-25 was found in this dataset. However, if one assumes the existence of the *HPC1* locus, up to 2.6% of these 150 predominantly Caucasian families were estimated to be linked. When families potentially linked to other putative prostate cancer loci were removed, up to 19.8% of the 46 remaining predominantly Caucasian families were estimated to be linked (up to 6% of the total sample).

Although no subset of families had statistically significant evidence of linkage, evidence of heterogeneity was observed in selected subsets. Assuming heterogeneity among Caucasian families, up to 12.3% of families with a mean age at diagnosis of >65 years, 11.1% with a mean age at diagnosis of ≤65 years and five or more affected men, and 3.2% with a mean age at diagnosis of ≤65 years and prostate cancer in more than one generation were estimated to be linked to *HPC1*. When families potentially linked to other putative prostate cancer loci were removed and heterogeneity was assumed, up to 11.7% of remaining Caucasian families with a mean age of diagnosis of >65 years, 2.7% with a mean age at diagnosis of ≤65 years, and 14.7% with a mean age at diagnosis of ≤65 years and prostate cancer in more than one generation were estimated to be linked.

Discrepancies in linkage study results may be due to false-positive evidence of linkage, differences in analytic methods, and differences in study populations or samples. The first explanation is unlikely, given that support for linkage to the *HPC1* region was demonstrated in several studies. To address the issue of analytic methods, we tested for linkage using the models used by other groups to detect linkage, and we also used methods that were less model dependent. We still did not detect significant evidence for linkage in this dataset.

Differences in study populations can be harder to assess. The mean ages of onset, family size, and number of persons affected in this study closely resemble those of Smith et al. [1996]. However, there may be important measured or unmeasured differences between the samples.

Affected men participating in PROGRESS were diagnosed between 1974 and 1997, and 83% of cases were diagnosed in 1989 or later. Family recruitment by Smith et al. [1996] began in the mid-1980s [Walsh, 1998], before commonplace PSA screening. Adoption of PSA screening led to a sharp increase in new diagnoses of preclinical prostate cancer from 1989 to 1992 and to a decrease in the mean age at diagnosis of new cases [Merrill and Brawley, 1997]. If the proportion of cases detected by PSA screening is increased in our sample, cases with subclinical disease may have a greater representation than in the samples collected earlier. If *HPC1* leads to more aggressive disease, it may be less common in our sample and in others with more recent family collections, relative to those studies with longstanding collections.

It has been argued, in fact, that *HPC1* predisposes to advanced prostate cancer [Grönberg et al., 1997b]. Grönberg et al. compared age at diagnosis, PSA level, digital rectal exam status, stage, grade, primary treatment of prostate cancer cases in families "potentially linked" to *HPC1* to families "potentially unlinked" and to cases from the general population. They found that men in "potentially linked" families had lower mean age of diagnosis and more grade 3 cancers than men in "potentially unlinked" families and more stage III or IV cancers than the general population. Because of concerns about ascertainment bias, relevance of comparison groups, and lack of evidence for a linear trend, others argued against these conclusions [Laniado, 1998; Walther, 1998]. Nonetheless, date and method of diagnosis, stage at diagnosis, and measures of cancer progression need to be addressed in further studies of high-risk prostate cancer families.

Differences in the racial makeup of the sample may also be a factor in the differences in linkage results. Although the majority of families contributing to the significant lod score reported by Smith et al. [1996] were Caucasian, the African-American families studied had a total lod score of 1.4. Two subsequent studies supporting *HPC1* linkage each included six African-American families [Cooney et al., 1997; Hsieh et al., 1997]. The six African-American families studied by Cooney et al. [1997] yielded a maximum NPL score of 1.39 ($p = 0.08$). Although Hsieh et al. [1997] reported that analysis of six African-American families alone yielded insignificant NPL scores, younger-onset African-American families were included in the analysis that produced significant lod scores. In the present study, only two African-American families were analyzed. One of these had non-significant positive lod scores across the *HPC1* region. We are currently seeking the participation of additional African-American families.

Linkage at 1q24-25 is likely to be much less common across high-risk families than the 34% originally proposed [Smith et al., 1996]. In another study of 136 families (including 76 families with three or more affected men), it was estimated that 4% of families were linked, assuming heterogeneity [Eeles et al., 1998]. The latter number is consistent with our results. Until *HPC1* is cloned and sequenced and mutations in high-risk families can be identified, multiple populations of high-risk families must be studied in more detail to assess the role of this locus in hereditary prostate cancer. It is likely that additional prostate cancer susceptibility genes remain to be mapped since the four loci reported to date are unlikely to account for more than one half of the disease in high-risk families studied. Further linkage studies are required to locate additional hereditary prostate cancer loci.

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APPENDIX B. CHROMOSOMAL LOCATIONS OF MARKERS ANALYZED

Comprehensive genetic map (Sex-averaged distances in Kosambi cM) from the Marshfield Medical Research Foundation

Chromosome 1	Locus	Marker	Distance Between	Location
	CAPB	D1S1597		29.93
			3.82	
	CAPB	D1S407		33.75
			158.30	
	HPC1	D1S1589		192.05
			2.84	
	HPC1	D1S2883		194.89
			3.41	
	HPC1	D1S2818		198.30
			2.00	
	HPC1	D1S2127		200.30
			1.89	
	HPC1	D1S518		202.19
			10.25	
	HPC1	D1S1660		212.44
			42.20	
	PCaP	D1S235		254.64
			11.63	
	PCaP	D1S2785		266.27
			1.24	
	PCaP	D1S547		267.51
			7.02	
	PCaP	D1S1609		274.53
Chromosome X	*HPCX*	DXS984		
			5.2	
	HPCX	DXS8106		
			1.2	
	HPCX	DXS6806		
			3.1	
	HPCX	DXS1200		
			0.6	
	HPCX	DXS297		
			2.3	
	HPCX	DXS1193		
			1.2	
	HPCX	DXS8069		
			0.7	
	HPCX	DXS8103		

APPENDIX C. MEDICAL RECORD ABSTRACTION FORM

PROGRESS STUDY MEDICAL RECORDS ABSTRACT

FAMILY: «famno»
SUBJECT: «subID»
Medical Record Available? «med_rec»
DATE (M/D/Y): ___/___/____

1. CONFIRMATION OF PROSTATE CANCER: ..... ☐ 1 NO ☐ 2 YES
   IF YES, BASED ON (MAY SELECT MORE THAN ONE):
   - PATHOLOGY REPORT FROM BIOPSY (NEEDLE OR TURP)..... ☐ 1 NO ☐ 2 YES
   - PATHOLOGY REPORT FROM SURGERY..... ☐ 1 NO ☐ 2 YES
   - OPERATIVE REPORT..... ☐ 1 NO ☐ 2 YES
   - PHYSICIAN STATEMENT OF DIAGNOSIS..... ☐ 1 NO ☐ 2 YES
   - ELEVATED PSA..... ☐ 1 NO ☐ 2 YES

2. ADENOCARCINOMA: ..... ☐ 1 NO ☐ 2 YES
   If no, type: _____

3. DATE OF DIAGNOSIS:..... (M/D/Y) ___/___/____

4. PROSTATE SPECIFIC ANTIGEN LEVEL (PRE-DIAGNOSIS): ___ ___ ___ . ___ ☐ 999 UNK

5. DIGITAL RECTAL EXAM:.....
   NORMAL ☐ 1
   ABNORMAL ☐ 2
   UNKNOWN ☐ 9

6. TOTAL GLEASON SCORE: .....
   BIOPSY ___ ___ ☐ 99 UNK
   PROSTATECTOMY ___ ___ ☐ 99 UNK

7. TUMOR GRADE:
   WELL DIFF.; GLEASON 2-4; GRADE I ☐ 1
   MOD. DIFF.; GLEASON 5-7; GRADE II ☐ 2
   ANAPLASTIC; POORLY DIFF.; GLEASON 8-10; GRADE III, IV ☐ 3
   UNKNOWN ☐ 9

8. TNM CLINICAL STAGE OF DISEASE:..... T____N____M____ ☐ 999 UNK

9. JEWET CLINICAL STAGE OF DISEASE:
   A ☐ 1
   B ☐ 2
   C ☐ 3
   D1 ☐ 4
   D2 ☐ 5
   UNKNOWN ☐ 9

SUBJECT: ___ ___ ___ ___ ___ ___ -___

6. JEWET PATHOLOGIC STAGE OF DISEASE:

A ☐ 1
B ☐ 2
C ☐ 3
D1 ☐ 4
D2 ☐ 5
NO PROSTATECTOMY ☐ 6
UNKNOWN ☐ 9

11. LOCAL INVOLVEMENT (IF HAD PROSTATECTOMY):

SURGICAL MARGIN.....	☐ 1NEG	☐ 2POS	☐ 9UNK
EXTRACAPSULAR EXTENSION...	☐ 1NEG	☐ 2POS	☐ 9UNK
SEMINAL VESICLE	☐ 1NEG	☐ 2POS	☐ 9UNK

12. OTHER INVOLVEMENT:

LYMPH NODES	☐ 1NEG	☐ 2POS	☐ 9UNK
BONE SCAN.....	☐ 1NEG	☐ 2POS	☐ 9UNK
OTHER SITE _____	☐ 1NEG	☐ 2POS	☐ 9UNK

13. TREATMENT: (SELECT ONLY ONE PRIMARY, MAY SELECT MORE THAN ONE SECONDARY)

	1°	2°
RADICAL PROSTATECTOMY	☐ 1	☐ 1
RADIATION (EXTERNAL BEAM OR IMPLANT)	☐ 2	☐ 2
ORCHIECTOMY	☐ 3	☐ 3
HORMONES ALONE	☐ 4	☐ 4
HORMONES AFTER SURGERY	☐ 5	☐ 5
NO TREATMENT (WATCHFUL WAITING)	☐ 6	☐ 6
OTHER TREATMENT	☐ 7	☐ 7
NO ADDTIONAL TREATMENT	☐ 8	☐ 8
UNKNOWN	☐ 9	☐ 9

14. OTHER PRIMARY CANCERS: ..... 1 NO ☐ 2 YES ☐

14.1 SITE: _____ PATH CONFIRMED: 1 NO ☐ 2 YES ☐
TYPE: _____ ICD-2-CODE ___ ___.___
DATE OF DIAGNOSIS: (M/D/Y) ___/___/___

14.2 SITE: _____ PATH CONFIRMED: 1 NO ☐ 2 YES ☐
TYPE: _____ ICD-2-CODE ___ ___.___
DATE OF DIAGNOSIS: (M/D/Y) ___/___/___

14.3 SITE: _____ PATH CONFIRMED: 1 NO ☐ 2 YES ☐
TYPE: _____ ICD-2-CODE ___ ___.___
DATE OF DIAGNOSIS: (M/D/Y) ___/___/___

APPENDIX D. PROSTATE CANCER STAGING AND GRADING SYSTEMS

TABLE D-1. PROSTATE CANCER GRADE GROUPINGS

AJCC Grade	Amount of Differentiation	Gleason Score
I	High	2-4
II	Moderate	5-7
III, IV	Low	8-10

TABLE D-2. THE JEWETT STAGING SYSTEM

Stage A is clinically undetectable tumor confined to the prostate gland and is an incidental finding at prostatic surgery.
- Substage A1: well-differentiated with focal involvement, usually left untreated
- Substage A2: moderately or poorly differentiated or involves multiple foci in the gland

Stage B is tumor confined to the prostate gland.
- Substage B0: nonpalpable, PSA-detected
- Substage B1: single nodule in one lobe of the prostate
- Substage B2: more extensive involvement of one lobe or involvement of both lobes

Stage C is a tumor clinically localized to the periprostatic area but extending through the prostatic capsule; seminal vesicles may be involved.
- Substage C1: clinical extracapsular extension
- Substage C2: extracapsular tumor producing bladder outlet or ureteral obstruction

Stage D is metastatic disease.
- Substage D0: clinically localized disease (prostate only) but persistently elevated enzymatic serum acid phosphatase titers
- Substage D1: regional lymph nodes only
- Substage D2: distant lymph nodes, metastases to bone or visceral organs
- Substage D3: D2 prostate cancer patients who relapsed after adequate endocrine therapy

TABLE D-3. TNM STAGING SYSTEM

Primary tumor (T)
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Clinically inapparent tumor not palpable or visible by imaging
  - T1a: Tumor incidental histologic finding in 5% or less of tissue resected
  - T1b: Tumor incidental histologic finding in more than 5% of tissue resected
  - T1c: Tumor identified by needle biopsy (e.g., performed because of elevated PSA)
- T2: Tumor confined within prostate
  - T2a: Tumor involves half of a lobe or less
  - T2b: Tumor involves more than half of a lobe, but not both lobes
  - T2c: Tumor involves both lobes
- T3: Tumor extends through the prostatic capsule
  - T3a: Unilateral extracapsular extension
  - T3b: Bilateral extracapsular extension
  - T3c: Tumor invades seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures other than seminal vesicles
  - T4a: Tumor invades any of: bladder neck, external sphincter, or rectum
  - T4b: Tumor invades levator muscles and/or is fixed to pelvic wall

Regional lymph nodes (N)
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph node metastases, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)
- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Nonregional lymph node(s)
  - M1b: Bone(s)
  - M1c: Other site(s)

TABLE D-4. AJCC STAGE GROUPINGS

Stage 0
- T1a, N0, M0, well differentiated cells

Stage I
- T1a, N0, M0, moderately differentiated or undifferentiated cells
- T1b, N0, M0
- T1c, N0, M0
- T1, N0, M0

Stage II
- T2, N0, M0

Stage III
- T3, N0, M0

Stage IV
- T4, N0, M0
- any T, N1, M0
- any T, N2, M0
- any T, N3, M0
- any T, any N, M1

APPENDIX E. ADDITIONAL CLINICAL DATA ON AFFECTED MEN

TABLE E-1. YEAR OF DIAGNOSIS AND PSA LEVEL AT DIAGNOSIS*

Year of Diagnosis	Grouped PSA level (ng/ml) <4	4-<10	10-<20	20 +	Unknown	Total
1974	0	0	0	0	1	1
1975	0	0	0	0	2	2
1977	0	0	0	0	1	1
1978	0	0	0	0	1	1
1979	0	0	0	0	2	2
1980	0	0	0	0	2	2
1981	0	0	0	0	4	4
1982	0	0	0	0	5	5
1983	0	0	0	0	6	6
1984	0	0	0	0	4	4
1985	0	0	0	0	7	7
1986	0	0	0	0	13	13
1987	0	0	0	1	8	9
1988	1	3	0	3	10	17
1989	1	6	2	4	8	21
1990	1	8	3	8	14	34
1991	4	13	13	25	8	63
1992	4	19	20	16	16	75
1993	4	23	22	9	8	66
1994	4	26	15	6	4	55
1995	6	43	19	7	5	80
1996	1	13	1	3	0	18
1997	0	6	2	0	0	8
1998	0	4	2	0	2	8
1999	0	3	0	0	0	3
Total	26 (5%)	167 (33%)	99 (20%)	82 (16%)	131 (26%)	505

*PSA testing became available in the U.S. in 1986.

TABLE E-2. DISTRIBUTIONS OF TUMOR GRADE AND PSA LEVEL AT DIAGNOSIS*

Tumor Grade (Surg, if	Grouped PSA level (ng/ml)					
	<4	4-<10	10-<20	20 +	Unknown	Total
Well Differentiated	5	32	22	7	12	78
	1.09	7.00	4.81	1.53	2.63	17.07
Moderately Differenti	18	122	65	58	50	313
	3.94	26.70	14.22	12.69	10.94	68.49
Poorly Differentiated	2	10	10	14	4	40
	0.44	2.19	2.19	3.06	0.88	8.75
Unknown	1	3	2	3	17	26
	0.22	0.66	0.44	0.66	3.72	5.69
Total	26	167	99	82	83	457
	5.69	36.54	21.66	17.94	18.16	100.00

*Only including cases diagnosed after 1986, when PSA testing became available in the U.S.

TABLE E-3. DISTRIBUTIONS OF TUMOR GRADE AND ELEVATED PSA AT DIAGNOSIS*

Tumor Grade (Surg, if Avail.)	Elevated PSA		
	No/Unknown	Yes	Total
Well Differentiated	14	64	78
	3.06	14.00	17.07
Moderately Differenti	61	252	313
	13.35	55.14	68.49
Poorly Differentiated	4	36	40
	0.88	7.88	8.75
Unknown	17	9	26
	3.72	1.97	5.69
Total	96	361	457
	21.01	78.99	100.00

*Only including cases diagnosed after 1986, when PSA testing became available in the U.S.

TABLE E-4. SUMMARY STAGE AND PSA LEVEL AT DIAGNOSIS*

Summary Stage (Path, if Avail.)	Grouped PSA level (ng/ml) <4	4-<10	10-<20	20 +	Unknown	Total
Local	24	135	81	38	47	325
	5.25	29.54	17.72	8.32	10.28	71.12
Regional	2	24	10	26	18	80
	0.44	5.25	2.19	5.69	3.94	17.51
Distant	0	3	5	15	3	26
	0.00	0.66	1.09	3.28	0.66	5.69
Unknown	0	5	3	3	15	26
	0.00	1.09	0.66	0.66	3.28	5.69
Total	26	167	99	82	83	457
	5.69	36.54	21.66	17.94	18.16	100.00

*Only includes cases diagnosed after 1986, when PSA testing became available in the U.S.

TABLE E-5. CLINICAL STAGE AND PSA LEVEL AT DIAGNOSIS*

Clinical Stage)	Grouped PSA level (ng/ml) <4	4-<10	10-<20	20 +	Unknown	Total
Local	26	156	94	54	65	325
	5.69	34.14	20.57	11.82	14.22	71.12
Regional	0	5	1	11	2	80
	0.00	1.09	0.22	2.41	0.44	17.51
Distant	0	1	1	14	1	26
	0.00	0.22	0.22	3.06	0.22	5.69
Unknown	0	5	3	3	15	26
	0.00	1.09	0.66	0.66	3.28	5.69
Total	26	167	99	82	83	457
	5.69	36.54	21.66	17.94	18.16	100.00

Only includes cases diagnosed after 1986, when PSA testing became available in the U.S.

TABLE E-6. SUMMARY STAGE AND ELEVATED PSA AT DIAGNOSIS*

Summary Stage (Path, if Avail.)	Elevated PSA No/Unknown	Yes	Total
Local	63	262	325
	13.79	57.33	71.12
Regional	15	65	80
	3.28	14.22	17.51
Distant	3	23	26
	0.66	5.03	5.69
Unknown	15	11	26
	3.28	2.41	5.69
Total	96	361	457
	21.01	78.99	100.00

*Only includes cases diagnosed after 1986, when PSA testing became available in the U.S.

TABLE E-7. CROSS-TABULATION OF STAGE AND TUMOR GRADE

Summary Stage (Path, if Avail.)	Tumor Grade (Surg, if Avail.) Well Diff	Moderatel	Poorly Di	Unknown	Total
Local	71	244	21	17	353
	14.06	48.32	4.16	3.37	69.90
Regional	7	61	19	2	89
	1.39	12.08	3.76	0.40	17.62
Distant	2	22	5	0	29
	0.40	4.36	0.99	0.00	5.74
Unknown	8	11	0	15	34
	1.58	2.18	0.00	2.97	6.73
Total	88	338	45	34	505
	17.43	66.93	8.91	6.73	100.00

TABLE E-8. DISTRIBUTIONS OF TUMOR GRADE AND YEAR OF DIAGNOSIS

Yr of Dx Category	Tumor Differentiation (Surg, if Avail.) Well	Moderate	Poor	Unknown	Total
1974-1979	1	3	0	3	7
	0.20	0.59	0.00	0.59	1.39
1980-1984	7	9	2	3	21
	1.39	1.78	0.40	0.59	4.16
1985-1989	11	42	8	6	67
	2.18	8.32	1.58	1.19	13.27
1990-1994	46	198	28	21	293
	9.11	39.21	5.54	4.16	58.02
1995-1999	23	86	7	1	117
	4.55	17.03	1.39	0.20	23.17
Total	88	338	45	34	505
	17.43	66.93	8.91	6.73	100.00

TABLE E-9. DISTRIBUTIONS OF STAGE AND YEAR OF DIAGNOSIS

Yr of Dx Category	Summary Stage (Path, if Avail.) Local	Regional	Distant	Unknown	Total
1974-1979	4	0	1	2	7
	0.79	0.00	0.20	0.40	1.39
1980-1984	11	4	2	4	21
	2.18	0.79	0.40	0.79	4.16
1985-1989	41	18	4	4	67
	8.12	3.56	0.79	0.79	13.27
1990-1994	198	59	18	18	293
	39.21	11.68	3.56	3.56	58.02
1995-1999	99	8	4	6	117
	19.60	1.58	0.79	1.19	23.17
Total	353	89	29	34	505
	69.90	17.62	5.74	6.73	100.00

TABLE E-10. UPGRADING AT PROSTATECTOMY, GLEASON SCORE

Biopsy Gleason Score, Grouped	Surgery Gleason Score*, Grouped 2-4	5-6	7	8-10	Unknown	Total
2-4	8	18	2	2	4	34
	3.11	7.00	0.78	0.78	1.56	13.23
5-6	3	56	28	2	10	99
	1.17	21.79	10.89	0.78	3.89	38.52
7	0	6	16	7	3	32
	0.00	2.33	6.23	2.72	1.17	12.45
8-10	0	1	4	4	0	9
	0.00	0.39	1.56	1.56	0.00	3.50
Unknown	6	19	15	9	34	83
	2.33	7.39	5.84	3.50	13.23	32.30
Total	17	100	65	24	51	257
	6.61	38.91	25.29	9.34	19.84	100.00

*For men with known Gleason scores from biopsy and surgery grouped in this way, Kappa=0.25

TABLE E-11. UPGRADING AT PROSTATECTOMY, TUMOR GRADE

Biopsy Gleason Score, Grouped	Tumor Grade (Surg, if Avail.) Well Diff	Moderatel	Poorly Di	Unknown	Total
2-4	12	20	2	0	34
	4.67	7.78	0.78	0.00	13.23
5-6	3	93	3	0	99
	1.17	36.19	1.17	0.00	38.52
7	0	24	8	0	32
	0.00	9.34	3.11	0.00	12.45
8-10	0	5	4	0	9
	0.00	1.95	1.56	0.00	3.50
Unknown	13	50	10	10	83
	5.06	19.46	3.89	3.89	32.30
Total	28	192	27	10	257
	10.89	74.71	10.51	3.89	100.00

TABLE E-12. UPSTAGING AT PROSTATECTOMY

Clinical Stage	Pathologic Stage* Local	Regional	Distant	Unknown	Total
Local	160	63	11	20	254
	62.26	24.51	4.28	7.78	98.83
Regional	0	1	0	0	1
	0.00	0.39	0.00	0.00	0.39
Distant	0	0	1	0	1
	0.00	0.00	0.39	0.00	0.39
Total	160	64	12	20	257
	62.26	24.90	4.67	7.78	100.00

*For men with known clinical and pathologic stage, Kappa=0.66

APPENDIX F. ADDITIONAL CLINICAL DATA ON WHITE FAMILIES

TABLE F-1. MEDIAN AGE AT DIAGNOSIS AND MEDIAN YEAR AT DIAGNOSIS, WHITE FAMILIES

Median Age Dx	Grouped Median Dx Year 1985-1989	1990-1995	1995-1999	Total
<60 yrs	3	6	4	13
	2.10	4.20	2.80	9.09
60-64 yrs	4	27	3	34
	2.80	18.88	2.10	23.78
65-69 yrs	7	40	7	54
	4.90	27.97	4.90	37.76
70+ yrs	5	36	. 1	42
	3.50	25.17	0.70	29.37
Total	19	109	15	143
	13.29	76.22	10.49	100.00

TABLE F-2. MEDIAN AGE AT DIAGNOSIS AND MISSING MEDICAL RECORDS, WHITE FAMILIES

Median Age Dx	Men w/out Clinical Data		Total
	None	1+	
<60 yrs	4	9	13
	2.80	6.29	9.09
60-64 yrs	13	21	34
	9.09	14.69	23.78
65-69 yrs	18	36	54
	12.59	25.17	37.76
70+ yrs	25	17	42
	17.48	11.89	29.37
Total	60	83	143
	41.96	58.04	100.00

TABLE F-3. MEDIAN YEAR AT DIAGNOSIS AND MISSING MEDICAL RECORDS, WHITE FAMILIES

Grouped Median Dx Year	Men w/out Clinical Data		Total
	None	1+	
1985-1989	5	14	19
	3.50	9.79	13.29
1990-1995	51	58	109
	35.66	40.56	76.22
1995-1999	4	11	15
	2.80	7.69	10.49
Total	60	83	143
	41.96	58.04	100.00

TABLE F-4. GRADE AND STAGE, WHITE FAMILIES

Grouped Grade	Grouped Stage: All Local	Local/Reg	At Least	Total
Low & Low/Med	31	15	3	49
	21.68	10.49	2.10	34.27
All Medium	22	22	13	57
	15.38	15.38	9.09	39.86
At Least 1 High	10	18	9	37
	6.99	12.59	6.29	25.87
Total	63	55	25	143
	44.06	38.46	17.48	100.00

TABLE F-5. GRADE AND MEDIAN AGE AT DIAGNOSIS, WHITE FAMILIES

Grouped Grade	Grouped Median Age Dx <60 yrs	60-64 yrs	65-69 yrs	70+ yrs	Total
Low & Low/Med	3	8	18	20	49
	2.10	5.59	12.59	13.99	34.27
All Medium	9	17	22	9	57
	6.29	11.89	15.38	6.29	39.86
At Least 1 High	1	9	14	13	37
	0.70	6.29	9.79	9.09	25.87
Total	13	34	54	42	143
	9.09	23.78	37.76	29.37	100.00

TABLE F-6. GRADE AND MEDIAN YEAR AT DIAGNOSIS, WHITE FAMILIES

Grouped Grade	Grouped Median Dx Year 1985-1989	1990-1995	1995-1999	Total
Low & Low/Med	3	40	6	49
	2.10	27.97	4.20	34.27
All Medium	6	45	6	57
	4.20	31.47	4.20	39.86
At Least 1 High	10	24	3	37
	6.99	16.78	2.10	25.87
Total	19	109	15	143
	13.29	76.22	10.49	100.00

TABLE F-7. GRADE AND MISSING MEDICAL RECORDS, WHITE FAMILIES

Grouped Grade	Men w/out Clinical Data None	1+	Total
Low & Low/Med	24	25	49
	16.78	17.48	34.27
All Medium	20	37	57
	13.99	25.87	39.86
At Least 1 High	16	21	37
	11.19	14.69	25.87
Total	60	83	143
	41.96	58.04	100.00

TABLE F-8. STAGE AND MEDIAN AGE AT DIAGNOSIS, WHITE FAMILIES

Grouped Stage	Median Age Dx <60 yrs	60-64 yrs	65-69 yrs	70+ yrs	Total
All Local	5	16	20	22	63
	3.50	11.19	13.99	15.38	44.06
Local/Reg & Reg.	5	12	22	16	55
	3.50	8.39	15.38	11.19	38.46
At Least 1 Distant	3	6	12	4	25
	2.10	4.20	8.39	2.80	17.48
Total	13	34	54	42	143
	9.09	23.78	37.76	29.37	100.00

TABLE F-9. STAGE AND MEDIAN YEAR AT DIAGNOSIS, WHITE FAMILIES

Grouped Stage	Grouped Median Dx Year 1985-1989	1990-1995	1995-1999	Total
All Local	4	50	9	63
	2.80	34.97	6.29	44.06
Local/Reg & Reg.	6	46	3	55
	4.20	32.17	2.10	38.46
At Least 1 Distant	9	13	3	25
	6.29	9.09	2.10	17.48
Total	19	109	15	143
	13.29	76.22	10.49	100.00

TABLE F-10. STAGE AND MISSING MEDICAL RECORDS, WHITE FAMILIES

Grouped Stage	Men w/out Clinical Data None	1+	Total
All Local	29	34	63
	20.28	23.78	44.06
Local/Reg & Reg.	21	34	55
	14.69	23.78	38.46
At Least 1 Distant	10	15	25
	6.99	10.49	17.48
Total	60	83	143
	41.96	58.04	100.00

APPENDIX G. *HPC1* RESULTS SUBSTRATIFIED BY MEDIAN AGE AT DIAGNOSIS AND NUMBER OF AFFECTED MEN

TABLE G-1. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, MEDIAN AGE

Group	Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Median Age < 60	5+	4	D1S1589	0.012	0.34	0.012	0.34	-0.058	0.412	0.071	0.054	0.438
			D1S2883	0.012	0.34	0.012	0.34	-0.184	0.323	0.061	0.010	0.455
			D1S2818	0.210	0.16	0.210	0.16	-0.621	0.194	0.028	-0.188	0.541
			D1S2127	0.001	0.42	0.001	0.42	-0.653	0.206	0.031	-0.146	0.527
			D1S518	0.000	0.50	0.000	0.50	-0.671	0.222	0.034	-0.199	0.544
			D1S1660	0.000	0.50	0.000	0.50	-0.091	0.411	0.075	0.060	0.436
Median Age 60-64	5+	12	D1S1589	0.000	0.50	0.000	0.50	-2.869	0.000	-0.000	-0.503	0.667
			D1S2883	0.000	0.50	0.000	0.50	-2.470	0.001	-0.000	-0.311	0.587
			D1S2818	0.000	0.50	0.000	0.50	-2.620	0.001	-0.000	-0.211	0.545
			D1S2127	0.000	0.50	0.000	0.50	-2.764	0.000	-0.000	-0.267	0.569
			D1S518	0.000	0.50	0.000	0.50	-2.912	0.000	-0.000	-0.410	0.629
			D1S1660	0.008	0.36	0.008	0.36	-2.224	0.000	-0.000	-0.464	0.651
Median Age 65-69	5+	20	D1S1589	0.000	0.50	0.000	0.50	-1.969	0.039	-0.002	0.428	0.308
			D1S2883	0.173	0.22	0.218	0.00	-1.635	0.148	0.042	0.647	0.241
			D1S2818	0.173	0.22	0.218	0.00	-2.174	0.121	0.043	0.517	0.279
			D1S2127	0.450	0.08	0.450	0.08	-2.710	0.093	0.032	0.645	0.241
			D1S518	0.112	0.24	0.112	0.24	-3.170	0.001	-0.001	0.585	0.259
			D1S1660	0.091	0.28	0.091	0.28	-0.988	0.186	0.038	0.870	0.183
Median Age 70+	5+	11	D1S1589	0.000	0.50	0.000	0.50	0.292	0.776	0.313	0.887	0.181
			D1S2883	0.000	0.50	0.000	0.50	0.163	0.640	0.256	0.821	0.197
			D1S2818	0.000	0.50	0.000	0.50	0.839	0.997	0.838	0.958	0.166
			D1S2127	0.349	0.02	0.349	0.02	0.817	0.998	0.817	0.995	0.158
			D1S518	0.349	0.02	0.349	0.02	1.047	0.999	1.047	1.160	0.126
			D1S1660	0.044	0.26	0.044	0.26	0.558	0.996	0.556	0.445	0.305

TABLE G-2. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Low & Moderate Grade	< 65	11	D1S1589	0.155	0.16	0.185	0.00	-0.450	0.202	0.024	0.115	0.439
			D1S2883	0.000	0.50	0.000	0.50	-0.509	0.202	0.030	0.038	0.469
			D1S2818	0.108	0.18	0.108	0.18	-0.623	0.174	0.024	-0.031	0.496
			D1S2127	0.268	0.22	0.302	0.00	-0.610	0.178	0.025	-0.056	0.506
			D1S518	0.611	0.00	0.611	0.00	-0.513	0.214	0.035	0.021	0.475
			D1S1660	0.044	0.26	0.044	0.26	-0.459	0.227	0.035	0.091	0.448
	< 65, 5+	2	D1S1589	0.027	0.36	0.027	0.36	0.224	0.867	0.224	0.422	0.318
			D1S2883	0.027	0.36	0.027	0.36	0.220	0.792	0.228	0.408	0.333
			D1S2818	0.027	0.36	0.027	0.36	0.213	0.787	0.221	0.388	0.333
			D1S2127	0.009	0.36	0.009	0.36	0.262	0.912	0.261	0.464	0.318
			D1S518	0.005	0.36	0.007	0.12	0.341	0.996	0.341	0.581	0.299
			D1S1660	0.141	0.16	0.141	0.16	0.371	0.998	0.370	0.571	0.299
	>= 65	38	D1S1589	0.526	0.00	0.526	0.00	-1.961	0.012	0.004	-1.050	0.854
			D1S2883	0.062	0.22	0.109	0.00	-2.077	0.022	0.005	-0.387	0.641
			D1S2818	0.110	0.10	0.154	0.00	-2.731	0.002	0.001	-1.173	0.882
			D1S2127	0.000	0.50	0.000	0.50	-2.851	0.001	0.001	-1.198	0.888
			D1S518	0.000	0.50	0.000	0.50	-2.661	0.001	0.001	-1.032	0.850
			D1S1660	0.058	0.32	0.058	0.32	-1.543	0.002	0.002	-1.044	0.853
	>= 65, 5+	8	D1S1589	0.000	0.50	0.000	0.50	-1.175	0.001	-0.000	-0.324	0.585
			D1S2883	0.000	0.50	0.000	0.50	-1.313	0.001	-0.000	-0.394	0.615
			D1S2818	0.000	0.44	0.000	0.44	-1.380	0.002	-0.000	-0.467	0.646
			D1S2127	0.000	0.44	0.000	0.44	-1.393	0.002	-0.000	-0.426	0.628
			D1S518	0.098	0.20	0.098	0.20	-1.468	0.001	-0.000	-0.404	0.619
			D1S1660	0.098	0.20	0.098	0.20	-0.494	0.013	-0.002	-0.220	0.542
Moderate Grade Only	< 65	26	D1S1589	0.000	0.50	0.000	0.50	-2.458	0.003	-0.001	-1.086	0.863
			D1S2883	0.000	0.50	0.000	0.50	-2.387	0.006	-0.002	-1.169	0.881
			D1S2818	0.221	0.14	0.221	0.14	-3.536	0.001	-0.001	-1.148	0.877
			D1S2127	0.000	0.50	0.000	0.50	-3.741	0.000	-0.001	-1.367	0.919
			D1S518	0.122	0.24	0.122	0.24	-4.000	0.001	-0.001	-1.363	0.918
			D1S1660	0.000	0.50	0.000	0.50	-1.509	0.083	0.004	-0.490	0.679
	< 65, 5+	7	D1S1589	0.000	0.50	0.000	0.50	-0.313	0.363	0.085	0.554	0.260
			D1S2883	0.000	0.50	0.000	0.50	-0.063	0.462	0.133	0.581	0.253
			D1S2818	0.098	0.28	0.098	0.28	-0.622	0.238	0.041	0.329	0.332
			D1S2127	0.000	0.50	0.000	0.50	-0.762	0.204	0.031	0.288	0.346
			D1S518	0.000	0.50	0.000	0.50	-1.172	0.077	0.001	-0.081	0.487
			D1S1660	0.000	0.50	0.000	0.50	-0.798	0.033	-0.002	-0.212	0.541
	>= 65	31	D1S1589	0.015	0.32	0.063	0.00	-1.590	0.030	-0.004	0.649	0.251
			D1S2883	0.000	0.50	0.000	0.50	-1.863	0.060	0.000	0.596	0.267
			D1S2818	0.308	0.16	0.308	0.16	-2.591	0.000	-0.000	0.768	0.216

TABLE G-2 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S2127	0.001	0.42	0.001	0.42	-3.152	0.000	-0.000	0.855	0.193
			D1S518	0.385	0.18	0.407	0.00	-2.867	0.000	-0.001	1.117	0.133
			D1S1660	0.000	0.50	0.000	0.50	-1.670	0.031	-0.005	1.207	0.117
	>= 65, 5+	13	D1S1589	0.000	0.50	0.000	0.50	-0.403	0.313	0.083	0.657	0.240
			D1S2883	0.009	0.34	0.010	0.30	-0.118	0.438	0.214	0.920	0.175
			D1S2818	0.000	0.50	0.000	0.50	-1.257	0.001	-0.000	0.256	0.368
			D1S2127	0.021	0.38	0.021	0.38	-1.932	0.000	-0.000	0.256	0.368
			D1S518	0.142	0.00	0.142	0.00	-1.602	0.002	-0.001	0.642	0.244
			D1S1660	0.000	0.50	0.000	0.50	-0.275	0.387	0.105	1.141	0.130
At least 1 High-grade	< 65	10	D1S1589	0.004	0.38	0.004	0.38	-3.002	0.000	-0.000	-1.269	0.912
			D1S2883	0.000	0.50	0.000	0.50	-3.112	0.000	-0.000	-1.221	0.901
			D1S2818	0.003	0.42	0.003	0.42	-3.154	0.000	-0.000	-1.061	0.861
			D1S2127	0.011	0.30	0.011	0.30	-3.245	0.000	-0.000	-1.106	0.873
			D1S518	0.483	0.12	0.532	0.00	-3.112	0.000	-0.000	-0.898	0.813
			D1S1660	0.000	0.50	0.000	0.50	-2.243	0.000	-0.000	-0.563	0.693
	< 65, 5+	7	D1S1589	0.000	0.50	0.000	0.50	-2.839	0.000	0.000	-1.399	0.947
			D1S2883	0.000	0.50	0.000	0.50	-2.812	0.000	0.000	-1.199	0.905
			D1S2818	0.070	0.16	0.076	0.10	-2.833	0.000	0.000	-0.956	0.835
			D1S2127	0.000	0.50	0.000	0.50	-2.917	0.000	0.000	-0.997	0.848
			D1S518	0.000	0.50	0.000	0.50	-2.753	0.000	0.000	-0.917	0.822
			D1S1660	0.001	0.46	0.001	0.46	-1.888	0.000	0.000	-0.654	0.724
	>= 65	27	D1S1589	0.573	0.06	0.621	0.00	-1.605	0.014	-0.003	0.417	0.325
			D1S2883	0.573	0.06	0.621	0.00	-1.434	0.023	-0.004	0.674	0.242
			D1S2818	0.236	0.08	0.236	0.08	0.883	0.695	1.035	1.976	0.030
			D1S2127	0.186	0.12	0.186	0.12	0.217	0.513	0.626	1.704	0.050
			D1S518	0.216	0.06	0.216	0.06	-0.813	0.291	0.107	1.193	0.119
			D1S1660	0.189	0.20	0.189	0.20	-1.626	0.028	-0.004	0.527	0.288
	>= 65, 5+	10	D1S1589	0.189	0.20	0.189	0.20	-0.097	0.495	0.115	1.077	0.140
			D1S2883	0.189	0.20	0.189	0.20	-0.040	0.500	0.142	1.081	0.139
			D1S2818	0.159	0.16	0.159	0.16	1.303	0.995	1.301	1.861	0.047
			D1S2127	0.000	0.50	0.000	0.50	1.434	0.997	1.433	2.046	0.035
			D1S518	0.002	0.40	0.002	0.40	0.948	0.997	0.947	1.673	0.062
			D1S1660	0.000	0.50	0.000	0.50	0.339	0.798	0.350	0.593	0.250

TABLE G-3. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Local Stage Only	< 65	21	D1S1589	0.000	0.50	0.000	0.50	-2.458	0.000	-0.000	-1.213	0.891
			D1S2883	0.344	0.12	0.344	0.12	-2.604	0.000	-0.000	-1.335	0.914
			D1S2818	0.344	0.12	0.344	0.12	-3.081	0.000	-0.000	-1.307	0.909
			D1S2127	0.060	0.20	0.060	0.20	-2.971	0.000	-0.000	-1.176	0.883
			D1S518	0.000	0.50	0.018	0.00	-2.936	0.000	-0.000	-0.995	0.840
			D1S1660	0.001	0.46	0.003	0.00	-1.229	0.040	-0.003	-0.093	0.522
	< 65, 5+	4	D1S1589	0.032	0.24	0.032	0.24	0.078	0.549	0.144	0.135	0.382
			D1S2883	0.000	0.50	0.000	0.50	0.012	0.496	0.123	0.124	0.385
			D1S2818	0.074	0.30	0.074	0.30	-0.068	0.410	0.083	0.178	0.368
			D1S2127	0.000	0.50	0.022	0.00	-0.114	0.371	0.072	0.145	0.379
			D1S518	0.097	0.20	0.097	0.20	-0.216	0.299	0.051	-0.045	0.440
			D1S1660	0.023	0.28	0.062	0.00	-0.184	0.277	0.036	-0.048	0.441
	>= 65	42	D1S1589	0.002	0.46	0.002	0.46	-3.080	0.001	0.001	-0.668	0.742
			D1S2883	0.075	0.32	0.075	0.32	-2.800	0.005	0.003	0.119	0.441
			D1S2818	0.232	0.16	0.232	0.16	-2.364	0.059	0.002	-0.191	0.565
			D1S2127	0.036	0.34	0.036	0.34	-3.502	0.001	0.001	-0.689	0.749
			D1S518	0.039	0.32	0.039	0.32	-3.524	0.000	0.001	-0.455	0.667
			D1S1660	0.040	0.34	0.040	0.34	-3.006	0.000	0.001	-0.514	0.689
	>= 65, 5+	8	D1S1589	0.000	0.50	0.000	0.50	-1.346	0.000	-0.000	-0.162	0.519
			D1S2883	0.553	0.00	0.553	0.00	-1.305	0.019	-0.002	0.195	0.383
			D1S2818	0.010	0.34	0.010	0.34	-0.988	0.147	0.011	0.100	0.417
			D1S2127	0.004	0.46	0.004	0.46	-1.194	0.068	-0.000	-0.050	0.475
			D1S518	0.000	0.50	0.000	0.50	-1.028	0.135	0.008	0.281	0.353
			D1S1660	0.000	0.50	0.000	0.50	-0.169	0.296	0.019	0.484	0.287
Local & Regional Stage	< 65	17	D1S1589	0.000	0.50	0.000	0.50	-0.594	0.169	0.015	0.022	0.475
			D1S2883	0.090	0.20	0.090	0.20	-0.749	0.166	0.020	0.174	0.416
			D1S2818	0.019	0.32	0.019	0.32	-1.550	0.086	0.003	0.343	0.354
			D1S2127	0.157	0.12	0.207	0.00	-1.940	0.021	-0.003	-0.132	0.537
			D1S518	0.000	0.50	0.000	0.50	-1.965	0.031	-0.003	-0.090	0.520
			D1S1660	0.781	0.00	0.781	0.00	-1.111	0.069	-0.000	0.097	0.446
	< 65, 5+	6	D1S1589	0.042	0.34	0.042	0.34	-0.595	0.002	-0.000	-0.140	0.520
			D1S2883	0.042	0.34	0.042	0.34	-0.546	0.005	-0.001	0.123	0.417
			D1S2818	0.042	0.34	0.042	0.34	-1.054	0.002	-0.000	0.065	0.439
			D1S2127	0.000	0.50	0.000	0.50	-1.185	0.001	-0.000	0.000	0.463
			D1S518	0.000	0.50	0.000	0.50	-1.235	0.001	-0.000	-0.179	0.535
			D1S1660	0.000	0.50	0.000	0.50	-0.823	0.000	-0.000	-0.230	0.556
	>= 65	38	D1S1589	0.401	0.04	0.401	0.04	-1.936	0.027	-0.005	-0.633	0.730
			D1S2883	0.064	0.00	0.064	0.00	-1.708	0.096	0.011	-0.607	0.720
			D1S2818	0.117	0.04	0.117	0.04	-1.125	0.150	0.012	0.113	0.440

TABLE G-3 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S2127	0.376	0.00	0.376	0.00	-1.503	0.084	-0.002	0.363	0.345
			D1S518	0.000	0.50	0.000	0.50	-0.927	0.296	0.137	0.687	0.238
			D1S1660	0.518	0.00	0.518	0.00	-0.283	0.443	0.265	0.210	0.402
	>= 65, 5+	17	D1S1589	0.019	0.32	0.019	0.32	-0.215	0.450	0.212	0.450	0.226
			D1S2883	0.379	0.00	0.379	0.00	0.072	0.501	0.310	0.402	0.238
			D1S2818	0.010	0.34	0.010	0.34	-0.648	0.188	0.020	0.060	0.330
			D1S2127	0.140	0.16	0.140	0.16	-1.167	0.039	-0.003	0.195	0.292
			D1S518	0.465	0.10	0.490	0.00	-0.582	0.311	0.115	0.545	0.203
			D1S1660	1.101	0.00	1.101	0.00	0.046	0.517	0.327	0.420	0.233
At least 1 Distant Stage	< 65	9	D1S1589	0.000	0.50	0.000	0.50	-2.858	0.000	-0.000	-1.235	0.906
			D1S2883	0.000	0.50	0.000	0.50	-2.656	0.000	-0.000	-1.434	0.941
			D1S2818	0.000	0.50	0.000	0.50	-2.682	0.000	-0.000	-1.579	0.961
			D1S2127	0.000	0.50	0.000	0.50	-2.685	0.000	-0.000	-1.572	0.960
			D1S518	0.000	0.50	0.000	0.50	-2.724	0.000	-0.000	-1.595	0.963
			D1S1660	0.000	0.50	0.000	0.50	-1.872	0.000	-0.000	-1.316	0.922
	< 65, 5+	6	D1S1589	0.000	0.50	0.000	0.50	-2.411	0.000	0.000	-0.637	0.719
			D1S2883	0.000	0.50	0.000	0.50	-2.121	0.000	0.000	-0.657	0.727
			D1S2818	0.000	0.50	0.000	0.50	-2.119	0.000	0.000	-0.663	0.729
			D1S2127	0.000	0.50	0.000	0.50	-2.118	0.000	0.000	-0.617	0.711
			D1S518	0.000	0.50	0.000	0.50	-2.132	0.000	0.000	-0.527	0.674
			D1S1660	0.001	0.46	0.004	0.00	-1.307	0.002	0.000	-0.337	0.591
	>= 65	16	D1S1589	0.343	0.12	0.343	0.12	-0.139	0.445	0.102	1.887	0.038
			D1S2883	0.173	0.18	0.173	0.18	-0.866	0.043	-0.004	1.850	0.041
			D1S2818	0.000	0.50	0.000	0.50	-0.949	0.215	0.100	1.963	0.033
			D1S2127	0.172	0.22	0.217	0.00	-0.780	0.263	0.161	2.114	0.025
			D1S518	0.000	0.50	0.000	0.50	-1.891	0.000	-0.000	1.194	0.120
			D1S1660	0.000	0.50	0.000	0.50	-1.551	0.001	-0.000	1.265	0.108
	>= 65, 5+	6	D1S1589	0.118	0.20	0.118	0.20	-0.114	0.363	0.030	1.412	0.094
			D1S2883	0.305	0.08	0.305	0.08	-0.239	0.180	0.003	1.391	0.096
			D1S2818	0.000	0.50	0.000	0.50	0.302	0.617	0.399	2.022	0.039
			D1S2127	0.505	0.04	0.549	0.00	0.469	0.707	0.528	2.256	0.027
			D1S518	0.000	0.50	0.000	0.50	-0.512	0.010	-0.001	1.395	0.096
			D1S1660	0.000	0.50	0.000	0.50	-0.307	0.020	-0.002	0.925	0.171

TABLE G-4. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
No cases aggressive disease	< 65	19	D1S1589	0.069	0.32	0.069	0.32	-2.127	0.000	-0.000	-1.049	0.853
			D1S2883	0.000	0.50	0.000	0.50	-2.262	0.000	-0.000	-1.127	0.872
			D1S2818	0.180	0.00	0.198	0.00	-2.802	0.000	-0.000	-1.135	0.874
			D1S2127	0.672	0.06	0.672	0.06	-2.684	0.000	-0.000	-0.991	0.838
			D1S518	0.394	0.08	0.394	0.08	-2.589	0.000	-0.000	-0.861	0.802
			D1S1660	0.394	0.08	0.394	0.08	-0.992	0.092	0.001	-0.058	0.508
	< 65, 5+	3	D1S1589	0.394	0.08	0.394	0.08	0.421	0.997	0.420	0.555	0.260
			D1S2883	0.081	0.30	0.081	0.30	0.366	0.989	0.365	0.547	0.263
			D1S2818	0.081	0.30	0.081	0.30	0.222	0.790	0.229	0.519	0.269
			D1S2127	0.081	0.30	0.081	0.30	0.185	0.712	0.205	0.496	0.276
			D1S518	0.000	0.50	0.000	0.50	0.144	0.646	0.180	0.378	0.304
			D1S1660	0.000	0.50	0.000	0.50	0.069	0.539	0.120	0.214	0.342
	>= 65	34	D1S1589	0.000	0.50	0.000	0.50	-1.284	0.066	-0.004	-0.390	0.641
			D1S2883	0.465	0.10	0.490	0.00	-1.369	0.122	0.005	0.211	0.405
			D1S2818	0.066	0.20	0.066	0.20	-2.710	0.000	-0.001	-0.779	0.778
			D1S2127	0.007	0.34	0.007	0.34	-2.998	0.000	-0.000	-0.894	0.812
			D1S518	0.370	0.10	0.370	0.10	-2.610	0.000	-0.000	-0.545	0.699
			D1S1660	0.010	0.34	0.010	0.34	-1.502	0.001	-0.001	-0.170	0.555
	>= 65, 5+	6	D1S1589	0.160	0.20	0.160	0.20	-1.089	0.000	-0.000	-0.102	0.486
			D1S2883	0.000	0.50	0.000	0.50	-1.035	0.007	-0.001	0.136	0.399
			D1S2818	0.075	0.24	0.075	0.24	-1.662	0.000	-0.000	-0.606	0.684
			D1S2127	0.000	0.50	0.000	0.50	-1.851	0.000	-0.000	-0.722	0.733
			D1S518	0.597	0.12	0.638	0.00	-1.702	0.000	-0.000	-0.375	0.591
			D1S1660	0.026	0.26	0.026	0.26	-0.622	0.000	-0.000	0.071	0.422
Less than half cases aggressive disease	< 65	16	D1S1589	0.026	0.26	0.026	0.26	-1.624	0.003	-0.001	-0.540	0.694
			D1S2883	0.129	0.22	0.129	0.22	-1.179	0.016	-0.003	-0.429	0.652
			D1S2818	0.000	0.50	0.007	0.00	-1.169	0.058	-0.002	0.125	0.431
			D1S2127	0.000	0.50	0.007	0.00	-1.422	0.012	-0.002	-0.298	0.601
			D1S518	0.000	0.50	0.000	0.50	-1.751	0.005	-0.001	-0.267	0.588
			D1S1660	0.000	0.50	0.000	0.50	-1.067	0.025	-0.003	-0.010	0.485
	< 65, 5+	6	D1S1589	1.102	0.00	1.102	0.00	-1.279	0.000	-0.000	-0.281	0.575
			D1S2883	0.137	0.20	0.137	0.20	-0.675	0.002	-0.000	0.092	0.418
			D1S2818	0.586	0.14	0.586	0.14	-0.474	0.013	-0.001	0.415	0.300
			D1S2127	0.069	0.22	0.069	0.22	-0.515	0.008	-0.001	0.372	0.314
			D1S518	0.000	0.50	0.000	0.50	-0.898	0.001	-0.000	0.002	0.455
			D1S1660	0.027	0.20	0.027	0.20	-0.642	0.001	-0.000	-0.047	0.476
	>= 65	43	D1S1589	0.000	0.50	0.000	0.50	-3.398	0.001	-0.001	0.002	0.484
			D1S2883	0.002	0.46	0.002	0.46	-3.210	0.008	-0.003	0.133	0.432
			D1S2818	0.287	0.14	0.287	0.14	-0.863	0.359	0.407	1.209	0.115

TABLE G-4 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPC1*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S2127	0.334	0.12	0.334	0.12	-2.317	0.165	0.106	0.957	0.167
			D1S518	0.000	0.50	0.000	0.50	-3.853	0.001	-0.001	0.246	0.389
			D1S1660	0.000	0.50	0.000	0.50	-2.495	0.039	-0.004	0.355	0.349
	>= 65, 5+	18	D1S1589	0.380	0.00	0.380	0.00	-1.386	0.066	0.000	0.059	0.442
			D1S2883	0.202	0.22	0.202	0.22	-1.179	0.134	0.028	0.055	0.443
			D1S2818	0.196	0.08	0.196	0.08	-0.098	0.457	0.399	0.469	0.294
			D1S2127	0.250	0.14	0.250	0.14	-0.821	0.297	0.233	0.511	0.281
			D1S518	0.007	0.36	0.007	0.36	-1.803	0.005	-0.002	-0.068	0.493
			D1S1660	0.007	0.36	0.007	0.36	-0.407	0.370	0.150	0.436	0.305
Half or more cases aggressive disease	< 65	10	D1S1589	0.000	0.50	0.000	0.50	-2.160	0.000	-0.000	-0.702	0.748
			D1S2883	0.036	0.30	0.036	0.30	-2.567	0.000	-0.000	-0.885	0.808
			D1S2818	0.000	0.50	0.000	0.50	-3.342	0.000	-0.000	-1.406	0.930
			D1S2127	0.000	0.50	0.000	0.50	-3.491	0.000	-0.000	-1.484	0.942
			D1S518	0.009	0.32	0.009	0.32	-3.284	0.000	-0.000	-1.413	0.932
			D1S1660	0.749	0.04	0.755	0.00	-2.153	0.000	-0.000	-1.062	0.858
	< 65, 5+	6	D1S1589	0.000	0.50	0.000	0.50	-2.070	0.000	0.000	-0.721	0.747
			D1S2883	0.000	0.50	0.000	0.50	-2.345	0.000	0.000	-0.844	0.791
			D1S2818	0.000	0.50	0.000	0.50	-2.990	0.000	0.000	-1.143	0.884
			D1S2127	0.000	0.50	0.000	0.50	-3.087	0.000	0.000	-1.131	0.880
			D1S518	0.000	0.50	0.000	0.50	-2.829	0.000	0.000	-0.938	0.823
			D1S1660	0.000	0.50	0.000	0.50	-1.741	0.000	0.000	-0.658	0.723
	>= 65	16	D1S1589	0.000	0.46	0.000	0.46	-0.474	0.259	0.030	0.359	0.344
			D1S2883	0.533	0.04	0.534	0.02	-0.795	0.081	-0.003	0.533	0.285
			D1S2818	0.000	0.50	0.000	0.50	-0.865	0.076	-0.003	0.901	0.180
			D1S2127	0.000	0.50	0.000	0.50	-0.470	0.274	0.040	1.186	0.120
			D1S518	0.109	0.14	0.112	0.10	0.120	0.551	0.349	1.750	0.047
			D1S1660	0.109	0.14	0.112	0.10	-0.843	0.070	-0.003	0.386	0.335
	>= 65, 5+	7	D1S1589	1.215	0.00	1.215	0.00	0.799	0.999	0.799	1.836	0.048
			D1S2883	0.000	0.50	0.000	0.50	0.743	0.999	0.743	1.909	0.043
			D1S2818	0.000	0.50	0.000	0.50	0.426	0.955	0.423	1.884	0.045
			D1S2127	0.000	0.50	0.000	0.50	0.780	0.999	0.780	2.188	0.028
			D1S518	0.000	0.50	0.000	0.50	1.382	0.999	1.382	2.901	0.009
			D1S1660	0.025	0.28	0.025	0.28	0.599	0.998	0.598	1.263	0.109

APPENDIX H. *PCAP* RESULTS SUBSTRATIFIED BY MEDIAN AGE AT DIAGNOSIS AND NUMBER OF AFFECTED MEN

TABLE H-1. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, MEDIAN AGE

Group	Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Median Age < 60	5+	4	D1S235	0.000	0.50	0.000	0.50	-0.987	0.000	-0.000	-0.354	0.606
			D1S2785	0.601	0.00	0.601	0.00	-0.769	0.000	-0.000	-0.450	0.634
			D1S547	0.000	0.50	0.000	0.50	-1.296	0.000	-0.000	-0.596	0.676
			D1S1609	0.081	0.22	0.081	0.22	-0.521	0.001	-0.000	-0.243	0.568
Median Age 60-64	5+	12	D1S235	0.000	0.50	0.000	0.50	-2.640	0.004	-0.001	-0.651	0.725
			D1S2785	0.144	0.24	0.144	0.24	-1.862	0.026	-0.001	0.056	0.435
			D1S547	0.552	0.14	0.552	0.14	-1.755	0.029	-0.001	0.081	0.425
			D1S1609	0.010	0.34	0.031	0.00	-0.491	0.291	0.089	0.097	0.419
Median Age 65-69	5+	20	D1S235	0.000	0.50	0.000	0.50	-3.019	0.007	-0.002	-0.778	0.773
			D1S2785	0.588	0.18	0.673	0.00	-1.476	0.266	0.493	0.861	0.185
			D1S547	0.027	0.34	0.027	0.34	-1.690	0.248	0.450	0.800	0.200
			D1S1609	0.134	0.28	0.238	0.00	-1.282	0.303	0.694	1.241	0.111
Median Age 70+	5+	11	D1S235	0.086	0.18	0.086	0.18	-0.783	0.002	-0.001	0.237	0.373
			D1S2785	0.000	0.50	0.000	0.50	-0.371	0.005	-0.001	0.353	0.333
			D1S547	0.000	0.50	0.000	0.50	-0.274	0.012	-0.002	0.493	0.287
			D1S1609	0.823	0.00	0.823	0.00	-0.030	0.496	0.004	0.569	0.264

TABLE H-2. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Low & Moderate Grade	< 65	11	D1S235	0.052	0.20	0.052	0.20	-1.074	0.001	-0.000	-0.152	0.544
			D1S2785	0.000	0.50	0.000	0.50	-2.034	0.000	-0.000	-0.940	0.824
			D1S547	0.000	0.50	0.000	0.50	-2.329	0.000	-0.000	-0.922	0.819
			D1S1609	0.184	0.14	0.184	0.14	-0.814	0.001	-0.000	-0.394	0.640
	< 65, 5+	2	D1S235	0.003	0.30	0.003	0.30	-0.420	0.000	-0.000	0.166	0.400
			D1S2785	0.304	0.00	0.304	0.00	-0.244	0.001	-0.000	0.060	0.406
			D1S547	0.000	0.42	0.000	0.42	-0.783	0.000	-0.000	-0.134	0.475
			D1S1609	0.252	0.10	0.252	0.10	0.080	0.980	0.079	0.303	0.374
	>= 65	38	D1S235	0.062	0.20	0.062	0.20	-1.369	0.003	0.002	0.022	0.478
			D1S2785	0.042	0.28	0.056	0.00	-2.621	0.003	0.002	-0.574	0.710
			D1S547	0.030	0.30	0.030	0.30	-2.679	0.002	0.002	-0.647	0.735
			D1S1609	0.000	0.50	0.000	0.50	-3.357	0.000	0.001	-1.025	0.848
	>= 65, 5+	8	D1S235	0.000	0.50	0.000	0.50	-1.111	0.000	-0.000	-0.370	0.605
			D1S2785	0.000	0.50	0.000	0.50	-2.069	0.000	-0.000	-0.897	0.816
			D1S547	0.041	0.26	0.041	0.26	-2.064	0.000	-0.000	-0.749	0.761
			D1S1609	0.000	0.50	0.000	0.50	-2.254	0.000	-0.000	-0.780	0.773
Moderate Grade Only	< 65	26	D1S235	0.000	0.50	0.000	0.50	-2.510	0.006	-0.002	-0.987	0.838
			D1S2785	0.213	0.20	0.250	0.00	-1.373	0.178	0.069	-0.146	0.544
			D1S547	0.529	0.12	0.529	0.12	-1.241	0.188	0.073	-0.088	0.521
			D1S1609	0.045	0.24	0.099	0.00	-0.320	0.421	0.233	0.056	0.463
	< 65, 5+	7	D1S235	0.000	0.50	0.039	0.00	-0.833	0.154	0.042	-0.090	0.486
			D1S2785	0.195	0.18	0.214	0.00	-1.051	0.100	0.017	0.139	0.395
			D1S547	0.431	0.10	0.431	0.10	-1.059	0.092	0.014	0.129	0.399
			D1S1609	0.000	0.50	0.003	0.00	-0.568	0.208	0.038	-0.106	0.492
	>= 65	31	D1S235	0.000	0.50	0.000	0.50	-2.634	0.037	-0.000	-0.432	0.655
			D1S2785	0.011	0.38	0.011	0.38	-1.528	0.160	0.095	0.227	0.396
			D1S547	0.001	0.44	0.001	0.44	-1.797	0.131	0.069	0.151	0.425
			D1S1609	0.259	0.18	0.292	0.00	-0.274	0.397	0.562	1.004	0.158
	>= 65, 5+	13	D1S235	0.000	0.50	0.000	0.50	-1.607	0.092	0.020	-0.623	0.713
			D1S2785	0.036	0.30	0.036	0.30	-0.389	0.315	0.211	0.102	0.424
			D1S547	0.000	0.50	0.000	0.50	-0.558	0.276	0.182	0.029	0.452
			D1S1609	0.213	0.18	0.251	0.00	0.486	0.558	0.793	0.974	0.163
At least 1 High-grade	< 65	10	D1S235	0.000	0.50	0.000	0.50	-2.675	0.000	-0.000	-0.653	0.728
			D1S2785	0.217	0.18	0.217	0.18	-1.161	0.000	-0.000	0.452	0.299
			D1S547	0.267	0.18	0.267	0.18	-0.985	0.001	-0.000	0.513	0.280
			D1S1609	0.120	0.20	0.120	0.20	-0.215	0.321	0.031	0.779	0.205
	< 65, 5+	7	D1S235	0.000	0.50	0.000	0.50	-2.373	0.000	0.000	-1.119	0.884
			D1S2785	0.085	0.26	0.085	0.26	-1.335	0.000	0.000	-0.439	0.635
			D1S547	0.108	0.26	0.108	0.26	-1.209	0.000	0.000	-0.401	0.619

TABLE H-2 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S1609	0.015	0.34	0.015	0.34	-0.524	0.014	0.002	-0.112	0.497
	>= 65	27	D1S235	0.043	0.30	0.043	0.30	-2.609	0.000	-0.000	-1.286	0.907
			D1S2785	0.125	0.28	0.217	0.00	-1.421	0.156	0.163	-0.316	0.609
			D1S547	0.000	0.50	0.000	0.00	-1.334	0.181	0.199	-0.187	0.558
			D1S1609	0.025	0.32	0.130	0.00	-1.265	0.168	0.153	-0.451	0.661
	>= 65, 5+	10	D1S235	0.208	0.18	0.208	0.18	-1.084	0.001	-0.000	0.191	0.376
			D1S2785	0.947	0.00	0.947	0.00	0.611	0.664	0.678	2.275	0.025
			D1S547	0.000	0.50	0.059	0.00	0.657	0.701	0.708	2.286	0.025
			D1S1609	0.529	0.02	0.591	0.00	0.454	0.591	0.584	1.939	0.043

TABLE H-3. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Local Stage Only	< 65	21	D1S235	0.000	0.50	0.000	0.50	-3.737	0.000	-0.000	-1.189	0.886
			D1S2785	0.000	0.50	0.000	0.50	-3.401	0.000	-0.000	-1.188	0.886
			D1S547	0.000	0.44	0.000	0.44	-3.574	0.000	-0.000	-1.149	0.877
			D1S1609	0.012	0.34	0.038	0.00	-1.464	0.002	-0.001	-0.489	0.677
	< 65, 5+	4	D1S235	0.000	0.50	0.000	0.50	-1.721	0.000	-0.000	-0.953	0.845
			D1S2785	0.000	0.50	0.000	0.50	-1.415	0.000	-0.000	-0.837	0.791
			D1S547	0.008	0.32	0.008	0.32	-1.913	0.000	-0.000	-0.938	0.839
			D1S1609	0.000	0.50	0.010	0.00	-0.928	0.000	-0.000	-0.561	0.654
	>= 65	42	D1S235	0.000	0.50	0.000	0.50	-2.063	0.040	0.001	-0.260	0.592
			D1S2785	0.000	0.50	0.000	0.50	-2.875	0.054	0.010	-0.400	0.646
			D1S547	0.000	0.50	0.000	0.50	-2.755	0.063	0.015	-0.307	0.610
			D1S1609	0.000	0.50	0.015	0.00	-2.257	0.086	0.030	-0.207	0.571
	>= 65, 5+	8	D1S235	0.000	0.50	0.000	0.50	-0.606	0.239	0.101	0.352	0.325
			D1S2785	0.000	0.50	0.015	0.00	-0.633	0.298	0.203	0.755	0.210
			D1S547	0.000	0.50	0.000	0.50	-0.634	0.298	0.204	0.793	0.201
			D1S1609	0.127	0.12	0.234	0.00	-0.272	0.396	0.293	0.882	0.181
Local & Regional Stage	< 65	17	D1S235	0.000	0.50	0.000	0.50	-1.665	0.000	-0.000	-0.716	0.755
			D1S2785	0.923	0.00	0.923	0.00	-0.605	0.056	-0.004	0.443	0.318
			D1S547	0.250	0.16	0.250	0.16	-0.501	0.113	-0.003	0.515	0.294
			D1S1609	0.108	0.20	0.108	0.20	-0.357	0.302	0.043	0.605	0.265
	< 65, 5+	6	D1S235	0.000	0.50	0.000	0.50	-0.983	0.000	-0.000	-0.652	0.718
			D1S2785	0.725	0.00	0.725	0.00	-0.618	0.001	-0.000	0.005	0.458
			D1S547	0.081	0.24	0.081	0.24	-0.619	0.000	-0.000	-0.004	0.462
			D1S1609	0.001	0.46	0.001	0.46	-0.515	0.011	-0.001	0.114	0.417
	>= 65	38	D1S235	0.000	0.50	0.000	0.50	-3.618	0.000	-0.000	-0.686	0.748
			D1S2785	0.286	0.20	0.286	0.20	-1.929	0.007	-0.003	-0.553	0.701
			D1S547	0.088	0.24	0.088	0.24	-2.299	0.002	-0.001	-0.884	0.810
			D1S1609	0.001	0.36	0.007	0.20	-2.163	0.096	0.033	-0.643	0.733
	>= 65, 5+	17	D1S235	0.000	0.50	0.000	0.50	-2.736	0.000	-0.000	-0.589	0.524
			D1S2785	0.345	0.12	0.345	0.12	-0.967	0.004	-0.001	-0.131	0.388
			D1S547	0.214	0.16	0.214	0.16	-0.928	0.005	-0.001	-0.077	0.371
			D1S1609	0.199	0.20	0.199	0.20	-0.796	0.231	0.125	0.470	0.221
At least 1 Distant Stage	< 65	9	D1S235	0.033	0.24	0.186	0.00	-0.858	0.250	0.095	0.267	0.360
			D1S2785	0.209	0.18	0.209	0.18	-0.561	0.253	0.094	0.393	0.314
			D1S547	0.338	0.16	0.338	0.16	-0.480	0.275	0.103	0.417	0.306
			D1S1609	0.314	0.12	0.314	0.12	0.471	0.859	0.474	0.396	0.313
	< 65, 5+	6	D1S235	0.007	0.30	0.142	0.00	-0.922	0.220	0.080	0.219	0.353
			D1S2785	0.167	0.20	0.167	0.20	-0.597	0.208	0.063	0.389	0.293
			D1S547	0.307	0.18	0.307	0.18	-0.519	0.229	0.070	0.399	0.290

TABLE H-3 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S1609	0.261	0.12	0.261	0.12	0.431	0.924	0.429	0.283	0.330
	>= 65	16	D1S235	0.046	0.28	0.046	0.28	-0.932	0.014	-0.003	-0.759	0.767
			D1S2785	0.152	0.28	0.201	0.00	-0.766	0.256	0.301	0.522	0.287
			D1S547	0.019	0.34	0.051	0.00	-0.756	0.281	0.349	0.829	0.199
			D1S1609	0.212	0.18	0.298	0.00	-0.476	0.297	0.312	0.559	0.275
	>= 65, 5+	6	D1S235	0.167	0.16	0.167	0.16	-0.459	0.018	-0.002	-0.512	0.642
			D1S2785	0.244	0.22	0.310	0.00	-0.247	0.327	0.351	1.401	0.095
			D1S547	0.000	0.50	0.000	0.50	-0.402	0.299	0.320	1.344	0.102
			D1S1609	0.093	0.24	0.157	0.00	-0.244	0.316	0.303	1.227	0.119

TABLE H-4. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
No cases aggressive disease	< 65	19	D1S235	0.000	0.50	0.000	0.50	-3.394	0.000	-0.000	-1.307	0.909
			D1S2785	0.000	0.50	0.000	0.50	-3.075	0.000	-0.000	-1.392	0.923
			D1S547	0.008	0.34	0.008	0.34	-3.253	0.000	-0.000	-1.351	0.917
			D1S1609	0.116	0.16	0.141	0.00	-1.138	0.004	-0.001	-0.638	0.730
	< 65, 5+	3	D1S235	0.000	0.50	0.000	0.50	-1.346	0.000	-0.000	-0.593	0.670
			D1S2785	0.000	0.50	0.000	0.50	-1.048	0.000	-0.000	-0.488	0.607
			D1S547	0.050	0.22	0.050	0.22	-1.552	0.000	-0.000	-0.623	0.683
			D1S1609	0.088	0.12	0.114	0.00	-0.567	0.000	-0.000	-0.206	0.468
	>= 65	34	D1S1609	0.000	0.50	0.008	0.00	-0.724	0.215	0.082	0.125	0.439
			D1S2785	0.000	0.50	0.006	0.00	-1.886	0.127	0.062	-0.214	0.573
			D1S547	0.001	0.44	0.001	0.44	-1.816	0.136	0.070	-0.093	0.525
			D1S1609	0.000	0.50	0.030	0.00	-1.687	0.134	0.068	-0.132	0.541
	>= 65, 5+	6	D1S235	0.000	0.50	0.011	0.00	-0.007	0.453	0.221	0.376	0.317
			D1S2785	0.034	0.26	0.044	0.00	-0.594	0.307	0.214	0.478	0.286
			D1S547	0.007	0.36	0.007	0.36	-0.643	0.293	0.201	0.498	0.279
			D1S1609	0.002	0.32	0.095	0.00	-0.387	0.350	0.249	0.479	0.285
Less than half cases aggressive disease	< 65	16	D1S235	0.000	0.50	0.025	0.00	-0.697	0.174	0.047	-0.418	0.647
			D1S2785	0.213	0.20	0.213	0.20	-1.453	0.001	-0.001	-0.164	0.546
			D1S547	0.089	0.26	0.089	0.26	-1.332	0.002	-0.001	-0.100	0.520
			D1S1609	0.007	0.36	0.007	0.36	-0.596	0.229	0.044	0.063	0.455
	< 65, 5+	6	D1S235	0.000	0.50	0.000	0.50	-0.469	0.228	0.078	-0.580	0.695
			D1S2785	0.000	0.50	0.000	0.00	-1.238	0.000	-0.000	-0.436	0.636
			D1S547	0.050	0.22	0.000	0.50	-1.173	0.000	-0.000	-0.401	0.621
			D1S1609	0.088	0.12	0.114	0.00	-0.516	0.137	0.009	-0.168	0.521
	>= 65	43	D1S235	0.045	0.32	0.045	0.32	-3.811	0.000	-0.000	-0.563	0.705
			D1S2785	0.632	0.18	0.633	0.16	-1.786	0.195	0.257	0.552	0.281
			D1S547	0.116	0.24	0.153	0.12	-2.027	0.184	0.240	0.490	0.301
			D1S1609	0.275	0.22	0.297	0.00	-1.445	0.257	0.447	0.521	0.291
	>= 65, 5+	18	D1S235	0.076	0.28	0.076	0.28	-2.589	0.000	-0.000	-0.511	0.673
			D1S2785	0.988	0.08	0.988	0.08	0.092	0.447	0.500	1.475	0.079
			D1S547	0.176	0.18	0.206	0.08	0.000	0.430	0.481	1.495	0.076
			D1S1609	0.613	0.14	0.613	0.14	0.370	0.500	0.820	1.971	0.036
Half or more cases aggressive disease	< 65	10	D1S235	0.000	0.50	0.000	0.50	-2.168	0.000	-0.000	-0.068	0.502
			D1S2785	0.765	0.04	0.765	0.04	-0.040	0.474	0.212	1.238	0.112
			D1S547	0.494	0.12	0.494	0.12	0.029	0.499	0.241	1.271	0.106
			D1S1609	0.409	0.06	0.409	0.06	0.385	0.850	0.386	1.147	0.127
	< 65, 5+	6	D1S235	0.000	0.50	0.000	0.50	-1.811	0.000	0.000	-0.195	0.531
			D1S2785	0.383	0.10	0.388	0.04	-0.344	0.281	0.094	0.456	0.291
			D1S547	0.226	0.18	0.226	0.18	-0.325	0.289	0.095	0.435	0.297

TABLE H-4 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *PCAP*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			D1S1609	0.081	0.18	0.081	0.18	0.071	0.536	0.134	0.234	0.365
	>= 65	16	D1S235	0.000	0.50	0.000	0.50	-2.078	0.000	-0.000	-1.372	0.922
			D1S2785	0.000	0.50	0.000	0.50	-1.899	0.000	-0.000	-1.443	0.933
			D1S547	0.000	0.50	0.000	0.50	-1.966	0.000	-0.000	-1.559	0.949
			D1S1609	0.000	0.50	0.000	0.50	-1.764	0.000	-0.000	-1.312	0.911
	>= 65, 5+	7	D1S235	0.000	0.50	0.000	0.50	-1.205	0.000	-0.000	-0.545	0.678
			D1S2785	0.000	0.50	0.000	0.50	-1.345	0.000	-0.000	-0.909	0.817
			D1S547	0.000	0.50	0.000	0.50	-1.321	0.000	-0.000	-0.887	0.809
			D1S1609	0.000	0.50	0.000	0.50	-1.296	0.000	-0.000	-0.792	0.775

APPENDIX I. *HPCX* RESULTS SUBSTRATIFIED BY MEDIAN AGE AT DIAGNOSIS AND NUMBER OF AFFECTED MEN

TABLE I-1. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, MODE OF TRANSMISSION

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Male-Male Transmission	< 65	27	DXS984	0.030	0.34	0.030	0.34	-1.771	0.001	-0.001	0.911	0.179
			DXS8106	0.000	0.50	0.000	0.50	-2.054	0.080	0.009	0.981	0.162
			DXS6806	0.043	0.30	0.056	0.00	-1.920	0.104	0.026	1.090	0.139
			DXS1200	0.000	0.50	0.000	0.00	-2.296	0.002	-0.001	-0.036	0.500
			DXS297	0.016	0.30	0.025	0.00	-2.359	0.001	-0.001	-0.168	0.553
			DXS1193	0.000	0.50	0.000	0.50	-2.634	0.045	0.003	0.149	0.427
			DXS8069	0.220	0.06	0.245	0.00	-2.808	0.038	0.001	-0.264	0.591
			DXS8103	0.012	0.46	0.012	0.46	-2.890	0.037	0.001	-0.244	0.583
	< 65, 5+	11	DXS984	0.133	0.18	0.133	0.18	-1.265	0.000	-0.000	0.354	0.331
			DXS8106	0.000	0.50	0.000	0.50	-1.489	0.115	0.023	0.787	0.206
			DXS6806	0.165	0.20	0.167	0.10	-1.356	0.145	0.047	0.939	0.167
			DXS1200	0.388	0.02	0.396	0.00	-1.394	0.012	-0.002	0.555	0.273
			DXS297	0.269	0.08	0.269	0.08	-1.440	0.003	-0.001	0.470	0.298
			DXS1193	0.000	0.46	0.000	0.46	-1.748	0.105	0.033	0.957	0.163
			DXS8069	0.334	0.00	0.334	0.00	-1.856	0.101	0.031	0.925	0.171
			DXS8103	0.023	0.42	0.040	0.00	-1.941	0.099	0.030	0.905	0.176
	>= 65	51	DXS984	0.000	0.50	0.000	0.50	-0.451	0.312	0.098	0.286	0.375
			DXS8106	0.000	0.50	0.000	0.50	-0.393	0.338	0.151	0.073	0.456
			DXS6806	0.000	0.50	0.000	0.50	-0.899	0.183	0.045	-0.444	0.660
			DXS1200	0.000	0.50	0.021	0.00	-1.796	0.148	0.041	0.172	0.418
			DXS297	0.000	0.50	0.000	0.50	-1.675	0.133	0.030	0.145	0.428
			DXS1193	0.003	0.46	0.003	0.46	-2.302	0.016	-0.004	-0.220	0.573
			DXS8069	0.000	0.50	0.000	0.50	-2.428	0.010	-0.004	-0.533	0.693
			DXS8103	0.000	0.50	0.000	0.50	-3.164	0.000	-0.001	-1.123	0.871
	>= 65, 5+	22	DXS984	0.000	0.50	0.000	0.50	-0.444	0.229	0.039	-0.019	0.468
			DXS8106	0.000	0.50	0.000	0.50	-0.206	0.353	0.118	0.249	0.368

TABLE I-1 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, MODE OF TRANSMISSION

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS6806	0.000	0.50	0.000	0.50	-0.684	0.143	0.021	-0.234	0.554
			DXS1200	0.000	0.50	0.024	0.00	-1.571	0.108	0.018	0.557	0.268
			DXS297	0.000	0.50	0.003	0.00	-1.400	0.099	0.014	0.570	0.264
			DXS1193	0.004	0.46	0.004	0.46	-1.654	0.023	-0.002	0.288	0.355
			DXS8069	0.000	0.50	0.000	0.50	-1.680	0.020	-0.002	0.201	0.385
			DXS8103	0.000	0.50	0.000	0.50	-2.333	0.000	-0.000	-0.669	0.726
Not Male-Male	< 65	5	DXS984	0.472	0.16	0.681	0.00	-0.395	0.079	-0.001	-0.017	0.436
			DXS8106	0.000	0.50	0.000	0.50	-0.956	0.000	-0.000	-0.261	0.564
			DXS6806	0.023	0.40	0.023	0.40	-1.272	0.000	-0.000	-0.341	0.619
			DXS1200	0.014	0.38	0.014	0.38	-1.284	0.000	-0.000	-0.344	0.619
			DXS297	0.000	0.46	0.000	0.46	-1.302	0.000	-0.000	-0.353	0.619
			DXS1193	0.042	0.18	0.119	0.00	-1.269	0.000	-0.000	-0.348	0.619
			DXS8069	0.093	0.18	0.163	0.00	-1.274	0.000	-0.000	-0.350	0.619
			DXS8103	0.089	0.32	0.089	0.32	-1.299	0.000	-0.000	-0.357	0.619
	< 65, 5+	3	DXS984	1.021	0.00	1.021	0.00	0.200	0.940	0.198	0.447	0.267
			DXS8106	0.000	0.50	0.000	0.50	-0.211	0.004	-0.000	0.116	0.452
			DXS6806	0.168	0.18	0.168	0.18	-0.524	0.000	-0.000	0.014	0.487
			DXS1200	0.007	0.42	0.007	0.42	-0.524	0.000	-0.000	0.014	0.487
			DXS297	0.007	0.40	0.007	0.40	-0.524	0.000	-0.000	0.013	0.487
			DXS1193	0.372	0.00	0.372	0.00	-0.492	0.000	-0.000	0.019	0.487
			DXS8069	0.617	0.00	0.617	0.00	-0.496	0.000	-0.000	0.017	0.487
			DXS8103	0.157	0.20	0.157	0.20	-0.524	0.000	-0.000	0.009	0.487
	>= 65	10	DXS984	0.000	0.46	0.000	0.46	-1.097	0.001	-0.000	0.010	0.449
			DXS8106	0.000	0.50	0.000	0.50	-1.115	0.001	-0.000	-0.258	0.539
			DXS6806	0.020	0.38	0.020	0.38	-1.126	0.001	-0.000	-0.310	0.562
			DXS1200	0.000	0.50	0.000	0.50	-1.081	0.002	-0.000	-0.179	0.507
			DXS297	0.081	0.18	0.113	0.00	-1.094	0.002	-0.001	-0.169	0.506
			DXS1193	0.000	0.50	0.004	0.00	-1.003	0.002	-0.001	-0.153	0.498
			DXS8069	0.000	0.46	0.000	0.46	-0.996	0.002	-0.001	-0.151	0.497
			DXS8103	0.042	0.30	0.047	0.00	-1.317	0.001	-0.000	-0.214	0.525
	>= 65, 5+	4	DXS984	0.000	0.50	0.000	0.50	-1.112.	0.000	-0.000	-0.670	0.739
			DXS8106	0.000	0.50	0.000	0.50	-1.216	0.000	-0.000	-0.740	0.787
			DXS6806	0.019	0.38	0.019	0.38	-1.179	0.000	-0.000	-0.736	0.787
			DXS1200	0.000	0.50	0.000	0.50	-1.049	0.000	-0.000	-0.705	0.787
			DXS297	0.145	0.14	0.145	0.14	-1.029	0.000	-0.000	-0.696	0.743
			DXS1193	0.000	0.50	0.000	0.50	-0.982	0.000	-0.000	-0.695	0.743
			DXS8069	0.000	0.50	0.000	0.50	-0.984	0.000	-0.000	-0.696	0.743
			DXS8103	0.001	0.46	0.001	0.46	-1.335	0.000	-0.000	-0.851	0.852

TABLE I-1 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, MODE OF TRANSMISSION

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Siblings Only	< 65	15	DXS984	0.154	0.22	0.302	0.00	-1.307	0.025	-0.003	0.365	0.354
			DXS8106	0.000	0.50	0.000	0.50	-2.203	0.000	-0.000	-0.563	0.665
			DXS6806	0.000	0.50	0.000	0.50	-2.015	0.000	-0.000	-0.588	0.710
			DXS1200	0.000	0.50	0.000	0.50	-1.913	0.000	-0.000	-0.586	0.710
			DXS297	0.000	0.50	0.000	0.50	-1.737	0.000	-0.000	-0.574	0.665
			DXS1193	0.002	0.36	0.008	0.00	-1.193	0.002	-0.001	-0.072	0.541
			DXS8069	0.013	0.22	0.013	0.22	-1.054	0.003	-0.001	0.048	0.435
			DXS8103	0.000	0.50	0.000	0.50	-1.078	0.002	-0.001	0.079	0.427
	< 65, 5+	2	DXS984	0.112	0.24	0.249	0.00	-0.795	0.041	-0.001	1.006	0.195
			DXS8106	0.000	0.50	0.000	0.50	-1.224	0.000	-0.000	-0.626	0.765
			DXS6806	0.000	0.50	0.000	0.50	-0.998	0.000	-0.000	-0.626	0.765
			DXS1200	0.000	0.50	0.000	0.50	-0.898	0.000	-0.000	-0.619	0.765
			DXS297	0.000	0.50	0.000	0.50	-0.722	0.000	-0.000	-0.587	0.414
			DXS1193	0.000	0.50	0.000	0.50	-0.417	0.000	-0.000	-0.434	0.414
			DXS8069	0.076	0.00	0.076	0.00	-0.424	0.000	-0.000	-0.379	0.414
			DXS8103	0.000	0.50	0.000	0.50	-0.507	0.000	-0.000	-0.377	0.414
	>= 65	33	DXS984	0.086	0.20	0.086	0.20	-0.489	0.196	0.011	-0.486	0.674
			DXS8106	0.014	0.30	0.016	0.02	-0.956	0.018	-0.005	-1.081	0.860
			DXS6806	0.000	0.50	0.000	0.50	-0.929	0.022	-0.005	-1.114	0.866
			DXS1200	1.237	0.00	1.237	0.00	0.078	0.499	0.268	-0.087	0.518
			DXS297	0.000	0.50	0.000	0.50	-0.502	0.227	0.048	-0.517	0.687
			DXS1193	0.000	0.50	0.000	0.50	-1.381	0.003	-0.002	-1.103	0.866
			DXS8069	0.005	0.32	0.005	0.32	-1.663	0.001	-0.001	-1.147	0.875
			DXS8103	0.000	0.50	0.000	0.50	-1.683	0.001	-0.001	-1.226	0.889
	>= 65, 5+	5	DXS984	0.330	0.00	0.330	0.00	0.000	0.500	0.045	0.049	0.450
			DXS8106	0.000	0.50	0.000	0.50	-0.165	0.228	0.005	-0.320	0.497
			DXS6806	0.000	0.50	0.000	0.50	-0.194	0.179	0.001	-0.383	0.548
			DXS1200	0.749	0.00	0.749	0.00	0.820	0.999	0.820	1.210	0.111
			DXS297	0.075	0.00	0.075	0.00	0.771	0.999	0.771	1.106	0.111
			DXS1193	0.000	0.50	0.000	0.50	0.294	0.994	0.293	0.085	0.450
			DXS8069	0.000	0.40	0.000	0.40	-0.051	0.395	0.016	-0.257	0.497
			DXS8103	0.000	0.50	0.000	0.50	-0.050	0.396	0.015	-0.250	0.497
Not Male-Male and Sibs Only	< 65	20	DXS984	0.473	0.16	0.682	0.00	-1.703	0.029	-0.003	0.307	0.369
			DXS8106	0.000	0.50	0.000	0.50	-3.160	0.000	-0.000	-0.618	0.716
			DXS6806	0.023	0.40	0.023	0.40	-3.288	0.000	-0.000	-0.679	0.747
			DXS1200	0.014	0.38	0.014	0.38	-3.198	0.000	-0.000	-0.680	0.747
			DXS297	0.000	0.46	0.000	0.46	-3.039	0.000	-0.000	-0.674	0.746
			DXS1193	0.043	0.18	0.120	0.00	-2.462	0.000	-0.000	-0.237	0.579
			DXS8069	0.094	0.18	0.163	0.00	-2.329	0.000	-0.000	-0.133	0.540

TABLE I-1 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, MODE OF TRANSMISSION

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS8103	0.090	0.32	0.090	0.32	-2.377	0.000	-0.000	-0.109	0.522
	< 65, 5+	5	DXS984	0.726	0.06	0.981	0.00	-0.595	0.331	0.066	0.983	0.166
			DXS8106	0.000	0.50	0.000	0.50	-1.435	0.000	-0.000	-0.306	0.614
			DXS6806	0.050	0.34	0.050	0.34	-1.522	0.000	-0.000	-0.384	0.641
			DXS1200	0.006	0.44	0.006	0.44	-1.423	0.000	-0.000	-0.380	0.641
			DXS297	0.004	0.46	0.004	0.46	-1.246	0.000	-0.000	-0.360	0.639
			DXS1193	0.026	0.10	0.106	0.00	-0.910	0.000	-0.000	-0.259	0.566
			DXS8069	0.693	0.00	0.693	0.00	-0.920	0.000	-0.000	-0.226	0.554
			DXS8103	0.049	0.36	0.049	0.36	-1.032	0.000	-0.000	-0.231	0.554
	>= 65	43	DXS984	0.005	0.42	0.005	0.42	-1.586	0.016	-0.005	-0.423	0.651
			DXS8106	0.000	0.50	0.000	0.50	-2.071	0.003	-0.002	-1.076	0.859
			DXS6806	0.005	0.46	0.005	0.46	-2.056	0.003	-0.002	-1.129	0.872
			DXS1200	0.922	0.00	0.922	0.00	-1.003	0.218	0.083	-0.161	0.548
			DXS297	0.000	0.50	0.001	0.16	-1.597	0.073	0.000	-0.535	0.692
			DXS1193	0.000	0.50	0.000	0.50	-2.385	0.001	-0.001	-1.045	0.852
			DXS8069	0.001	0.46	0.001	0.46	-2.659	0.001	-0.001	-1.083	0.861
			DXS8103	0.004	0.46	0.004	0.46	-3.000	0.000	-0.001	-1.182	0.884
	>= 65, 5+	9	DXS984	0.000	0.50	0.000	0.50	-1.111	0.000	-0.000	-0.410	0.623
			DXS8106	0.000	0.50	0.000	0.50	-1.382	0.000	-0.000	-0.732	0.703
			DXS6806	0.008	0.44	0.008	0.44	-1.374	0.000	-0.000	-0.776	0.712
			DXS1200	0.445	0.04	0.445	0.04	-0.229	0.372	0.145	0.431	0.282
			DXS297	0.196	0.12	0.196	0.12	-0.257	0.357	0.121	0.360	0.304
			DXS1193	0.000	0.50	0.000	0.50	-0.688	0.009	-0.001	-0.400	0.622
			DXS8069	0.000	0.50	0.000	0.50	-1.035	0.001	-0.000	-0.656	0.677
			DXS8103	0.000	0.50	0.000	0.50	-1.385	0.000	-0.000	-0.754	0.709

TABLE I-2. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, MEDIAN AGE

Group	Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Median Age < 60	5+	4	DXS984	0.000	0.50	0.000	0.50	-0.549	0.000	-0.000	0.128	0.323
			DXS8106	0.000	0.50	0.000	0.00	-0.564	0.356	0.154	1.100	0.198
			DXS6806	0.000	0.50	0.000	0.50	-0.493	0.382	0.205	1.341	0.131
			DXS1200	0.003	0.40	0.036	0.00	-0.745	0.227	0.034	0.604	0.217
			DXS297	0.020	0.28	0.092	0.00	-0.809	0.160	0.011	0.487	0.260
			DXS1193	0.111	0.22	0.156	0.00	-1.823	0.000	-0.000	-0.198	0.592
			DXS8069	0.000	0.50	0.018	0.00	-1.941	0.000	-0.000	-0.229	0.608
			DXS8103	0.000	0.50	0.000	0.50	-2.031	0.000	-0.000	-0.248	0.656
Median Age 60-64	5+	12	DXS984	0.000	0.50	0.000	0.50	-1.310	0.078	-0.000	0.899	0.175
			DXS8106	0.000	0.50	0.000	0.00	-2.360	0.000	-0.000	-0.079	0.487
			DXS6806	0.000	0.50	0.000	0.50	-2.385	0.000	-0.000	-0.123	0.507
			DXS1200	0.003	0.40	0.036	0.00	-2.072	0.000	-0.000	-0.062	0.480
			DXS297	0.020	0.28	0.092	0.00	-1.877	0.000	-0.000	-0.063	0.480
			DXS1193	0.111	0.22	0.156	0.00	-0.835	0.140	0.050	0.863	0.183
			DXS8069	0.000	0.50	0.018	0.00	-0.835	0.141	0.050	0.872	0.181
			DXS8103	0.000	0.50	0.000	0.50	-0.942	0.129	0.044	0.861	0.184
Median Age 64-69	5+	20	DXS984	0.000	0.50	0.000	0.50	-1.250	0.003	-0.001	0.087	0.422
			DXS8106	0.000	0.50	0.000	0.00	-1.314	0.004	-0.001	0.126	0.408
			DXS6806	0.000	0.50	0.000	0.50	-1.775	0.000	-0.000	-0.404	0.616
			DXS1200	0.003	0.40	0.036	0.00	-1.936	0.083	0.011	0.246	0.365
			DXS297	0.020	0.28	0.092	0.00	-1.822	0.047	-0.000	0.113	0.413
			DXS1193	0.111	0.22	0.156	0.00	-2.489	0.000	-0.000	-0.651	0.716
			DXS8069	0.000	0.50	0.018	0.00	-2.874	0.000	-0.000	-0.968	0.831
			DXS8103	0.000	0.50	0.000	0.50	-3.255	0.000	-0.000	-1.158	0.885
Median Age 70+	5+	11	DXS984	0.078	0.22	0.078	0.22	-0.037	0.440	0.056	-0.316	0.578
			DXS8106	0.000	0.50	0.000	0.50	-0.325	0.272	0.052	-0.133	0.499
			DXS6806	0.000	0.50	0.000	0.50	-0.309	0.288	0.064	-0.061	0.472
			DXS1200	0.293	0.06	0.349	0.00	0.114	0.538	0.257	1.229	0.119
			DXS297	0.825	0.00	0.825	0.00	0.131	0.550	0.273	1.331	0.104
			DXS1193	0.545	0.00	0.545	0.00	0.018	0.500	0.227	1.178	0.127
			DXS8069	0.092	0.12	0.242	0.00	-0.023	0.497	0.212	1.203	0.123
			DXS8103	0.000	0.46	0.000	0.46	-0.305	0.016	-0.002	0.314	0.346

TABLE I-3. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Low & Moderate Grade	< 65	11	DXS984	0.043	0.22	0.043	0.22	-0.661	0.001	-0.000	0.601	0.266
			DXS8106	0.000	0.50	0.000	0.50	-1.678	0.000	-0.000	0.068	0.447
			DXS6806	0.000	0.50	0.000	0.50	-1.668	0.000	-0.000	0.101	0.420
			DXS1200	0.004	0.44	0.004	0.44	-1.812	0.000	-0.000	-0.633	0.731
			DXS297	0.007	0.34	0.007	0.34	-1.829	0.000	-0.000	-0.749	0.791
			DXS1193	0.000	0.50	0.000	0.50	-1.810	0.000	-0.000	-0.709	0.791
			DXS8069	0.044	0.10	0.050	0.00	-1.870	0.000	-0.000	-1.312	0.927
			DXS8103	0.000	0.50	0.000	0.50	-1.861	0.000	-0.000	-1.245	0.887
	< 65, 5+	2	DXS984	0.067	0.16	0.067	0.16	-0.420	0.000	-0.000	-0.336	0.289
			DXS8106	0.000	0.50	0.000	0.50	-1.282	0.000	-0.000	-0.660	0.890
			DXS6806	0.000	0.50	0.000	0.50	-1.280	0.000	-0.000	-0.660	0.890
			DXS1200	0.065	0.12	0.067	0.00	-1.261	0.000	-0.000	-0.658	0.632
			DXS297	0.097	0.10	0.097	0.10	-1.262	0.000	-0.000	-0.658	0.632
			DXS1193	0.000	0.50	0.000	0.50	-1.282	0.000	-0.000	-0.659	0.890
			DXS8069	0.217	0.00	0.217	0.00	-1.281	0.000	-0.000	-0.659	0.632
			DXS8103	0.000	0.50	0.000	0.50	-1.282	0.000	-0.000	-0.659	0.890
	>= 65	38	DXS984	0.330	0.00	0.330	0.00	0.021	0.499	0.153	0.268	0.380
			DXS8106	0.000	0.50	0.000	0.50	-0.731	0.053	-0.006	-0.821	0.791
			DXS6806	0.000	0.50	0.000	0.50	-0.877	0.026	-0.005	-0.958	0.826
			DXS1200	0.749	0.00	0.749	0.00	-0.700	0.087	-0.005	-0.414	0.650
			DXS297	0.075	0.00	0.075	0.00	-0.911	0.024	-0.005	-0.452	0.663
			DXS1193	0.000	0.50	0.000	0.50	-2.091	0.000	-0.001	-0.853	0.799
			DXS8069	0.000	0.40	0.000	0.40	-2.171	0.000	-0.001	-0.934	0.820
			DXS8103	0.000	0.50	0.000	0.50	-2.264	0.000	-0.001	-1.102	0.866
	>= 65, 5+	8	DXS984	0.000	0.50	0.000	0.50	0.056	0.527	0.073	-0.623	0.656
			DXS8106	0.000	0.50	0.000	0.00	-0.090	0.325	0.019	-0.763	0.689
			DXS6806	0.000	0.50	0.000	0.50	-0.111	0.289	0.014	-0.732	0.682
			DXS1200	0.000	0.50	0.020	0.04	0.005	0.499	0.066	-0.138	0.530
			DXS297	0.000	0.50	0.000	0.50	-0.037	0.476	0.042	-0.061	0.490
			DXS1193	0.000	0.46	0.000	0.46	-0.700	0.000	-0.000	-0.394	0.622
			DXS8069	0.000	0.50	0.000	0.50	-0.707	0.000	-0.000	-0.401	0.622
			DXS8103	0.000	0.50	0.000	0.00	-0.709	0.000	-0.000	-0.405	0.622
Moderate Grade Only	< 65	26	DXS984	0.000	0.50	0.000	0.50	-2.210	0.002	-0.001	0.292	0.372
			DXS8106	0.000	0.50	0.000	0.00	-1.930	0.136	0.042	0.492	0.300
			DXS6806	0.128	0.26	0.187	0.00	-1.690	0.158	0.070	0.553	0.280
			DXS1200	0.002	0.40	0.002	0.40	-2.086	0.016	-0.003	-0.210	0.569
			DXS297	0.000	0.50	0.000	0.50	-2.007	0.007	-0.002	-0.277	0.594

TABLE I-3 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS1193	0.035	0.28	0.035	0.28	-2.524	0.000	-0.001	-0.264	0.590
			DXS8069	0.017	0.32	0.017	0.32	-2.530	0.001	-0.001	-0.202	0.565
			DXS8103	0.000	0.50	0.000	0.50	-2.646	0.000	-0.001	-0.196	0.564
	< 65, 5+	7	DXS984	0.000	0.50	0.000	0.50	-1.268	0.000	-0.000	0.404	0.303
			DXS8106	0.000	0.46	0.000	0.46	-0.468	0.397	0.183	1.176	0.131
			DXS6806	0.428	0.10	0.516	0.00	-0.179	0.451	0.250	1.348	0.092
			DXS1200	0.031	0.20	0.031	0.20	-0.389	0.304	0.055	0.689	0.224
			DXS297	0.174	0.00	0.174	0.00	-0.290	0.284	0.032	0.576	0.239
			DXS1193	0.000	0.50	0.000	0.50	-1.041	0.000	-0.000	-0.017	0.478
			DXS8069	0.186	0.00	0.186	0.00	-1.154	0.000	-0.000	-0.020	0.483
			DXS8103	0.000	0.50	0.000	0.50	-1.322	0.000	-0.000	-0.039	0.491
	>= 65	31	DXS984	0.037	0.36	0.037	0.36	-1.566	0.003	-0.002	-0.158	0.542
			DXS8106	0.001	0.46	0.001	0.46	-1.550	0.005	-0.002	0.086	0.445
			DXS6806	0.024	0.38	0.024	0.38	-1.821	0.001	-0.001	-0.124	0.529
			DXS1200	0.179	0.20	0.247	0.00	-1.427	0.189	0.067	0.927	0.175
			DXS297	0.000	0.50	0.000	0.50	-1.705	0.068	0.001	0.422	0.322
			DXS1193	0.000	0.50	0.000	0.50	-1.925	0.001	-0.001	-0.040	0.495
			DXS8069	0.000	0.50	0.000	0.50	-2.340	0.000	-0.000	-0.487	0.671
			DXS8103	0.007	0.44	0.007	0.44	-2.342	0.000	-0.000	-0.566	0.701
	>= 65, 5+	13	DXS984	0.000	0.50	0.000	0.50	-1.434	0.000	-0.000	-0.344	0.592
			DXS8106	0.000	0.50	0.000	0.50	-1.511	0.000	-0.000	-0.240	0.550
			DXS6806	0.014	0.42	0.014	0.42	-1.871	0.000	-0.000	-0.755	0.758
			DXS1200	0.094	0.26	0.149	0.00	-1.509	0.084	0.009	0.541	0.270
			DXS297	0.046	0.32	0.046	0.32	-1.319	0.063	0.002	0.488	0.286
			DXS1193	0.000	0.50	0.000	0.50	-1.229	0.001	-0.000	0.081	0.425
			DXS8069	0.000	0.50	0.000	0.50	-1.608	0.000	-0.000	-0.229	0.546
			DXS8103	0.004	0.46	0.004	0.46	-1.618	0.000	-0.000	-0.342	0.591
At least 1 High-grade	< 65	10	DXS984	1.119	0.00	1.119	0.00	-0.603	0.135	0.006	0.829	0.192
			DXS8106	0.000	0.50	0.000	0.50	-1.605	0.000	-0.000	-0.128	0.512
			DXS6806	0.033	0.36	0.033	0.36	-1.849	0.000	-0.000	-0.168	0.529
			DXS1200	0.000	0.50	0.000	0.50	-1.595	0.000	-0.000	-0.018	0.462
			DXS297	0.003	0.44	0.003	0.44	-1.561	0.000	-0.000	0.002	0.453
			DXS1193	0.000	0.50	0.047	0.00	-0.762	0.152	0.057	1.080	0.139
			DXS8069	0.482	0.00	0.493	0.00	-0.735	0.157	0.060	1.079	0.139
			DXS8103	0.161	0.60	0.161	0.60	-0.760	0.153	0.058	1.065	0.141
	< 65, 5+	7	DXS984	1.548	0.00	1.548	0.00	-0.171	0.406	0.088	1.050	0.148
			DXS8106	0.000	0.50	0.000	0.50	-1.173	0.000	0.000	-0.095	0.482
			DXS6806	0.053	0.32	0.053	0.32	-1.419	0.000	0.000	-0.142	0.505
			DXS1200	0.032	0.28	0.032	0.28	-1.166	0.000	0.000	0.037	0.421

TABLE I-3 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS297	0.004	0.44	0.004	0.44	-1.133	0.000	0.000	0.060	0.411
			DXS1193	0.057	0.20	0.146	0.00	-0.335	0.261	0.123	1.350	0.099
			DXS8069	0.624	0.00	0.624	0.00	-0.340	0.260	0.122	1.341	0.099
			DXS8103	0.226	0.26	0.226	0.26	-0.369	0.252	0.118	1.332	0.100
	>= 65	27	DXS984	0.000	0.50	0.000	0.50	-0.943	0.070	-0.002	-0.530	0.687
			DXS8106	0.000	0.50	0.000	0.00	-0.945	0.155	0.029	-0.523	0.684
			DXS6806	0.000	0.50	0.000	0.50	-0.996	0.152	0.030	-0.824	0.789
			DXS1200	0.003	0.40	0.036	0.00	-1.424	0.105	0.014	-0.538	0.690
			DXS297	0.020	0.28	0.092	0.00	-1.374	0.117	0.019	-0.436	0.651
			DXS1193	0.111	0.22	0.156	0.00	-1.289	0.134	0.026	-0.474	0.665
			DXS8069	0.000	0.50	0.018	0.00	-1.194	0.157	0.036	-0.328	0.609
			DXS8103	0.000	0.50	0.000	0.50	-1.802	0.001	-0.001	-0.909	0.814
	>= 65, 5+	10	DXS984	0.000	0.50	0.000	0.50	-0.627	0.034	-0.002	0.112	0.403
			DXS8106	0.000	0.50	0.000	0.50	-0.749	0.098	0.006	0.344	0.313
			DXS6806	0.000	0.50	0.000	0.50	-0.814	0.093	0.006	0.340	0.315
			DXS1200	0.014	0.32	0.065	0.00	-1.049	0.121	0.019	0.542	0.260
			DXS297	0.052	0.20	0.171	0.00	-1.019	0.131	0.023	0.551	0.257
			DXS1193	0.054	0.24	0.142	0.00	-1.031	0.126	0.021	0.413	0.293
			DXS8069	0.000	0.50	0.076	0.00	-1.019	0.130	0.022	0.464	0.279
			DXS8103	0.000	0.50	0.000	0.50	-1.635	0.000	-0.000	-0.550	0.653

TABLE I-4. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
Local Stage Only	< 65	21	DXS984	0.000	0.50	0.034	0.00	-1.770	0.024	-0.003	0.601	0.266
			DXS8106	0.000	0.50	0.000	0.50	-3.482	0.000	-0.000	-0.062	0.501
			DXS6806	0.025	0.42	0.025	0.42	-3.519	0.000	-0.000	0.094	0.450
			DXS1200	0.020	0.40	0.020	0.40	-3.584	0.000	-0.000	-0.325	0.615
			DXS297	0.013	0.42	0.013	0.42	-3.424	0.000	-0.000	-0.306	0.613
			DXS1193	0.000	0.50	0.100	0.00	-2.865	0.000	-0.000	0.145	0.434
			DXS8069	0.132	0.16	0.192	0.00	-2.928	0.000	-0.000	-0.249	0.583
			DXS8103	0.052	0.38	0.052	0.38	-3.010	0.000	-0.000	-0.240	0.581
	< 65, 5+	4	DXS984	0.000	0.50	0.088	0.00	-1.056	0.012	-0.001	-0.275	0.450
			DXS8106	0.000	0.50	0.000	0.50	-2.247	0.000	-0.000	-0.609	0.810
			DXS6806	0.031	0.40	0.031	0.40	-2.334	0.000	-0.000	-0.891	0.891
			DXS1200	0.062	0.28	0.062	0.28	-2.226	0.000	-0.000	-0.888	0.891
			DXS297	0.111	0.18	0.111	0.18	-2.053	0.000	-0.000	-0.870	0.810
			DXS1193	0.000	0.50	0.039	0.00	-1.742	0.000	-0.000	-0.756	0.777
			DXS8069	0.810	0.00	0.810	0.00	-1.738	0.000	-0.000	-0.718	0.730
			DXS8103	0.060	0.36	0.060	0.36	-1.843	0.000	-0.000	-0.722	0.730
	>= 65	42	DXS984	0.471	0.12	0.471	0.12	0.703	0.815	0.707	0.520	0.292
			DXS8106	0.000	0.50	0.003	0.26	-0.541	0.321	0.158	-0.375	0.631
			DXS6806	0.000	0.50	0.000	0.50	-0.676	0.286	0.138	-0.408	0.643
			DXS1200	0.062	0.24	0.195	0.00	-1.682	0.123	0.023	-0.176	0.554
			DXS297	0.037	0.28	0.052	0.00	-1.570	0.094	0.009	-0.253	0.585
			DXS1193	0.359	0.12	0.359	0.12	-1.622	0.059	0.001	-0.229	0.576
			DXS8069	0.017	0.30	0.057	0.00	-1.724	0.045	0.003	-0.567	0.705
			DXS8103	0.000	0.50	0.000	0.50	-2.066	0.000	0.001	-1.133	0.872
	>= 65, 5+	8	DXS984	0.311	0.14	0.311	0.14	0.791	0.998	0.790	0.949	0.170
			DXS8106	0.041	0.24	0.041	0.24	0.316	0.657	0.416	0.897	0.182
			DXS6806	0.020	0.30	0.020	0.30	0.311	0.648	0.417	0.978	0.164
			DXS1200	0.038	0.26	0.114	0.00	-0.461	0.392	0.224	0.879	0.185
			DXS297	0.445	0.00	0.445	0.00	-0.183	0.433	0.235	0.905	0.180
			DXS1193	0.475	0.06	0.475	0.06	-0.372	0.327	0.127	0.903	0.181
			DXS8069	0.008	0.32	0.086	0.00	-0.396	0.323	0.125	0.921	0.177
			DXS8103	0.000	0.50	0.000	0.50	-0.671	0.003	-0.001	-0.132	0.498
Local & Regional Stage	< 65	17	DXS984	0.733	0.06	0.733	0.06	-0.586	0.050	-0.004	0.509	0.297
			DXS8106	0.000	0.50	0.000	0.50	-0.540	0.216	0.067	0.287	0.366
			DXS6806	0.000	0.50	0.000	0.50	-0.630	0.198	0.075	0.215	0.395
			DXS1200	0.006	0.42	0.006	0.42	-1.020	0.012	-0.002	-0.492	0.682
			DXS297	0.000	0.50	0.000	0.50	-1.086	0.004	-0.001	-0.556	0.695
			DXS1193	0.003	0.44	0.007	0.00	-1.264	0.114	0.037	-0.066	0.507
			DXS8069	0.259	0.06	0.259	0.06	-1.239	0.127	0.044	-0.029	0.502

TABLE I-4 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS8103	0.039	0.36	0.114	0.00	-1.293	0.128	0.045	-0.026	0.502
	< 65, 5+	6	DXS984	1.140	0.00	1.140	0.00	0.195	0.863	0.193	1.502	0.083
			DXS8106	0.027	0.20	0.027	0.20	0.408	0.851	0.409	1.398	0.089
			DXS6806	0.587	0.06	0.587	0.06	0.399	0.779	0.409	1.546	0.075
			DXS1200	0.048	0.18	0.048	0.18	0.134	0.624	0.163	0.946	0.174
			DXS297	0.000	0.50	0.000	0.50	0.071	0.548	0.111	0.851	0.200
			DXS1193	0.034	0.28	0.058	0.00	-0.130	0.399	0.223	1.707	0.051
			DXS8069	0.338	0.00	0.338	0.00	-0.250	0.371	0.208	1.673	0.056
			DXS8103	0.040	0.34	0.153	0.00	-0.340	0.355	0.200	1.652	0.063
	>= 65	38	DXS984	0.000	0.50	0.000	0.50	-1.557	0.001	-0.001	-0.383	0.636
			DXS8106	0.000	0.50	0.000	0.50	-1.852	0.001	-0.001	-0.931	0.821
			DXS6806	0.000	0.50	0.000	0.50	-2.057	0.000	-0.001	-1.577	0.950
			DXS1200	0.009	0.26	0.101	0.00	-0.429	0.323	0.133	-0.342	0.620
			DXS297	0.027	0.36	0.027	0.36	-0.820	0.165	0.027	-0.627	0.725
			DXS1193	0.000	0.50	0.000	0.50	-2.213	0.000	-0.001	-1.524	0.943
			DXS8069	0.000	0.50	0.000	0.50	-2.562	0.000	-0.000	-1.540	0.945
			DXS8103	0.000	0.50	0.000	0.50	-2.978	0.000	-0.000	-1.693	0.962
	>= 65, 5+	17	DXS984	0.000	0.50	0.000	0.50	-1.146	0.000	-0.000	-0.465	0.645
			DXS8106	0.000	0.50	0.000	0.50	-1.476	0.000	-0.000	-0.711	0.741
			DXS6806	0.000	0.50	0.000	0.50	-1.796	0.000	-0.000	-1.323	0.919
			DXS1200	0.010	0.24	0.100	0.00	-0.342	0.287	0.080	0.675	0.237
			DXS297	0.088	0.24	0.088	0.24	-0.346	0.284	0.067	0.717	0.226
			DXS1193	0.000	0.50	0.000	0.50	-0.869	0.002	-0.001	-0.072	0.493
			DXS8069	0.000	0.50	0.000	0.50	-1.240	0.000	-0.000	-0.377	0.611
			DXS8103	0.000	0.50	0.000	0.50	-1.622	0.000	-0.000	-0.573	0.688
At least 1 Distant Stage	< 65	9	DXS984	0.002	0.44	0.026	0.00	-1.118	0.000	-0.000	0.419	0.316
			DXS8106	0.000	0.50	0.000	0.50	-1.190	0.000	-0.000	0.476	0.300
			DXS6806	0.000	0.50	0.000	0.50	-1.059	0.000	-0.000	0.434	0.312
			DXS1200	0.000	0.50	0.030	0.00	-0.889	0.000	-0.000	0.098	0.416
			DXS297	0.000	0.50	0.002	0.00	-0.887	0.000	-0.000	-0.065	0.489
			DXS1193	0.000	0.50	0.000	0.50	-0.967	0.000	-0.000	-0.225	0.559
			DXS8069	0.000	0.50	0.008	0.00	-0.969	0.000	-0.000	-0.236	0.563
			DXS8103	0.000	0.50	0.000	0.50	-0.963	0.000	-0.000	-0.182	0.542
	< 65, 5+	6	DXS984	0.008	0.06	0.101	0.00	-0.999	0.000	0.000	0.099	0.408
			DXS8106	0.000	0.50	0.000	0.50	-1.085	0.000	0.000	0.048	0.435
			DXS6806	0.000	0.50	0.000	0.50	-0.944	0.000	0.000	0.103	0.407
			DXS1200	0.016	0.14	0.079	0.00	-0.726	0.000	0.000	0.183	0.363
			DXS297	0.025	0.18	0.040	0.00	-0.705	0.000	0.000	0.167	0.372
			DXS1193	0.000	0.50	0.000	0.50	-0.786	0.000	0.000	-0.029	0.470

TABLE I-4 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS8069	0.000	0.50	0.000	0.50	-0.787	0.000	0.000	-0.040	0.478
			DXS8103	0.000	0.50	0.000	0.50	-0.789	0.000	0.000	-0.047	0.479
	>= 65	16	DXS984	0.008	0.46	0.008	0.46	-1.053	0.002	-0.001	-0.516	0.675
			DXS8106	0.000	0.46	0.000	0.46	-0.418	0.084	-0.004	0.130	0.421
			DXS6806	0.000	0.50	0.000	0.50	-0.573	0.042	-0.004	0.172	0.407
			DXS1200	0.225	0.08	0.233	0.00	-1.045	0.020	-0.003	0.651	0.246
			DXS297	0.000	0.50	0.000	0.50	-1.241	0.009	-0.002	0.554	0.273
			DXS1193	0.000	0.50	0.000	0.50	-1.268	0.008	-0.002	0.494	0.290
			DXS8069	0.000	0.50	0.000	0.46	-1.368	0.005	-0.001	0.494	0.290
			DXS8103	0.000	0.46	0.039	0.00	-1.331	0.006	-0.002	0.505	0.287
	>= 65, 5+	6	DXS984	0.000	0.50	0.000	0.50	-1.069	0.000	-0.000	-0.948	0.854
			DXS8106	0.000	0.50	0.000	0.50	-0.776	0.000	-0.000	-0.731	0.661
			DXS6806	0.000	0.50	0.000	0.50	-0.924	0.000	-0.000	-0.760	0.687
			DXS1200	0.007	0.32	0.007	0.32	-1.354	0.000	-0.000	-0.821	0.748
			DXS297	0.000	0.50	0.000	0.50	-1.487	0.000	-0.000	-0.918	0.811
			DXS1193	0.000	0.50	0.000	0.50	-1.518	0.000	-0.000	-0.918	0.811
			DXS8069	0.000	0.50	0.000	0.50	-1.647	0.000	-0.000	-0.918	0.811
			DXS8103	0.000	0.50	0.000	0.50	-1.635	0.000	-0.000	-0.912	0.811

TABLE I-5. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
No cases Aggressive Disease	< 65	19	DXS984	0.000	0.50	0.000	0.50	-2.142	0.001	-0.001	0.328	0.351
			DXS8106	0.000	0.50	0.000	0.50	-3.479	0.000	-0.000	-0.254	0.571
			DXS6806	0.000	0.50	0.000	0.50	-3.204	0.000	-0.000	-0.048	0.516
			DXS1200	0.000	0.50	0.000	0.50	-3.272	0.000	-0.000	-0.489	0.679
			DXS297	0.000	0.50	0.000	0.50	-3.112	0.000	-0.000	-0.469	0.678
			DXS1193	0.000	0.50	0.000	0.50	-2.586	0.000	-0.000	0.002	0.501
			DXS8069	0.000	0.50	0.000	0.50	-2.646	0.000	-0.000	-0.412	0.639
			DXS8103	0.000	0.50	0.000	0.50	-2.701	0.000	-0.000	-0.400	0.639
	< 65, 5+	3	DXS984	0.000	0.50	0.000	0.50	-1.412	0.000	-0.000	-0.505	0.487
			DXS8106	0.000	0.50	0.000	0.50	-2.229	0.000	-0.000	-0.832	0.912
			DXS6806	0.000	0.50	0.000	0.50	-2.003	0.000	-0.000	-0.823	0.912
			DXS1200	0.000	0.50	0.000	0.50	-1.895	0.000	-0.000	-0.819	0.912
			DXS297	0.079	0.14	0.079	0.14	-1.721	0.000	-0.000	-0.798	0.780
			DXS1193	0.352	0.00	0.352	0.00	-1.442	0.000	-0.000	-0.675	0.663
			DXS8069	0.000	0.50	0.000	0.50	-1.436	0.000	-0.000	-0.630	0.663
			DXS8103	0.144	0.00	0.144	0.00	-1.512	0.000	-0.000	-0.628	0.663
	>= 65	34	DXS984	0.374	0.08	0.374	0.08	0.449	0.825	0.444	0.198	0.402
			DXS8106	0.051	0.20	0.051	0.20	-0.334	0.274	0.034	-0.681	0.738
			DXS6806	0.000	0.50	0.000	0.50	-0.467	0.204	0.015	-0.710	0.750
			DXS1200	0.000	0.50	0.042	0.00	-1.155	0.077	-0.004	-0.201	0.559
			DXS297	0.000	0.50	0.000	0.50	-1.030	0.031	-0.005	-0.296	0.598
			DXS1193	0.073	0.22	0.073	0.22	-1.110	0.007	-0.003	-0.232	0.570
			DXS8069	0.007	0.26	0.008	0.20	-1.216	0.004	-0.002	-0.594	0.710
			DXS8103	0.000	0.50	0.000	0.50	-1.290	0.003	-0.002	-0.733	0.758
	>= 65, 5+	6	DXS984	0.191	0.12	0.191	0.12	0.395	0.992	0.393	0.171	0.372
			DXS8106	0.197	0.10	0.197	0.10	0.304	0.945	0.301	0.118	0.401
			DXS6806	0.154	0.12	0.154	0.12	0.280	0.907	0.277	0.158	0.376
			DXS1200	0.000	0.50	0.000	0.00	-0.543	0.254	0.034	-0.105	0.493
			DXS297	0.002	0.42	0.002	0.42	-0.254	0.303	0.036	-0.070	0.481
			DXS1193	0.068	0.22	0.068	0.22	-0.397	0.028	-0.002	-0.049	0.472
			DXS8069	0.000	0.50	0.000	0.50	-0.394	0.029	-0.002	-0.015	0.459
			DXS8103	0.000	0.42	0.000	0.42	-0.399	0.025	-0.002	-0.020	0.460
Less than half cases Aggressive Disease	< 65	16	DXS984	1.931	0.00	1.931	0.00	0.272	0.722	0.289	1.202	0.119
			DXS8106	0.000	0.50	0.000	0.50	-0.736	0.003	-0.001	0.316	0.360
			DXS6806	0.096	0.26	0.096	0.26	-1.105	0.001	-0.000	0.161	0.423
			DXS1200	0.049	0.28	0.049	0.28	-1.192	0.001	-0.000	-0.236	0.576
			DXS297	0.003	0.46	0.003	0.46	-1.226	0.000	-0.000	-0.381	0.629

TABLE I-5 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS1193	0.000	0.50	0.067	0.00	-1.228	0.000	-0.000	-0.506	0.686
			DXS8069	0.575	0.00	0.575	0.00	-1.116	0.000	-0.000	-0.458	0.659
			DXS8103	0.114	0.26	0.114	0.26	-1.101	0.001	-0.000	-0.391	0.635
	< 65, 5+	6	DXS984	1.948	0.00	1.948	0.00	0.621	0.998	0.620	1.709	0.050
			DXS8106	0.000	0.50	0.000	0.50	-0.218	0.015	-0.002	0.525	0.265
			DXS6806	0.226	0.18	0.226	0.18	-0.535	0.001	-0.000	0.436	0.314
			DXS1200	0.018	0.34	0.018	0.34	-0.566	0.001	-0.000	0.326	0.348
			DXS297	0.003	0.46	0.003	0.46	-0.578	0.001	-0.000	0.285	0.376
			DXS1193	0.105	0.06	0.166	0.00	-0.601	0.000	-0.000	0.117	0.435
			DXS8069	0.749	0.00	0.749	0.00	-0.605	0.000	-0.000	0.106	0.435
			DXS8103	0.050	0.36	0.050	0.36	-0.634	0.000	-0.000	0.095	0.435
	>= 65	43	DXS984	0.000	0.50	0.000	0.50	-1.242	0.076	-0.001	0.411	0.328
			DXS8106	0.000	0.50	0.000	0.50	-0.819	0.230	0.075	0.752	0.221
			DXS6806	0.000	0.50	0.000	0.50	-1.151	0.142	0.025	0.453	0.313
			DXS1200	0.000	0.50	0.034	0.00	-1.613	0.113	0.018	0.514	0.293
			DXS297	0.004	0.46	0.004	0.46	-2.190	0.026	-0.004	0.108	0.440
			DXS1193	0.000	0.50	0.000	0.50	-3.119	0.001	-0.001	-0.474	0.669
			DXS8069	0.000	0.50	0.000	0.50	-3.121	0.001	-0.001	-0.473	0.669
			DXS8103	0.000	0.50	0.000	0.50	-4.170	0.000	-0.000	-1.114	0.869
	>= 65, 5+	18	DXS984	0.000	0.50	0.000	0.50	-0.877	0.027	-0.003	0.381	0.321
			DXS8106	0.000	0.50	0.000	0.50	-0.837	0.090	0.004	0.415	0.310
			DXS6806	0.000	0.50	0.000	0.50	-1.313	0.006	-0.001	-0.181	0.526
			DXS1200	0.000	0.50	0.000	0.50	-1.602	0.016	-0.002	0.355	0.329
			DXS297	0.004	0.46	0.004	0.46	-1.744	0.010	-0.002	0.298	0.349
			DXS1193	0.000	0.50	0.000	0.50	-1.825	0.007	-0.001	0.133	0.408
			DXS8069	0.000	0.50	0.000	0.50	-1.851	0.006	-0.001	0.041	0.442
			DXS8103	0.000	0.50	0.000	0.50	-2.862	0.000	-0.000	-1.007	0.838
Half or more cases Aggressive Disease	< 65	10	DXS984	0.011	0.42	0.011	0.42	-1.606	0.000	-0.000	-0.036	0.490
			DXS8106	0.000	0.46	0.000	0.46	-0.998	0.098	0.015	0.626	0.255
			DXS6806	0.119	0.22	0.124	0.02	-0.898	0.122	0.033	0.631	0.253
			DXS1200	0.000	0.50	0.000	0.50	-1.030	0.003	-0.001	-0.042	0.492
			DXS297	0.000	0.50	0.000	0.50	-1.059	0.001	-0.000	-0.092	0.514
			DXS1193	0.007	0.42	0.007	0.42	-1.283	0.090	0.024	0.500	0.290
			DXS8069	0.271	0.00	0.271	0.00	-1.373	0.088	0.023	0.478	0.297
			DXS8103	0.028	0.40	0.028	0.40	-1.466	0.084	0.021	0.447	0.305
	< 65, 5+	6	DXS984	0.072	0.20	0.072	0.20	-1.069	0.000	0.000	0.023	0.435
			DXS8106	0.002	0.44	0.002	0.44	-0.476	0.229	0.072	0.786	0.210
			DXS6806	0.248	0.14	0.248	0.14	-0.339	0.263	0.109	0.987	0.164
			DXS1200	0.057	0.18	0.081	0.00	-0.356	0.143	0.008	0.609	0.248

TABLE I-5 (CONTINUED). SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *HPCX*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2pt lod	2pt θ	2pt hlod	2pt θ	Mpt lod	Mpt α	Mpt hlod	Mpt Npl	mpt p-value
			DXS297	0.036	0.22	0.036	0.18	-0.386	0.076	0.001	0.544	0.261
			DXS1193	0.011	0.40	0.011	0.40	-0.615	0.212	0.097	1.314	0.102
			DXS8069	0.132	0.00	0.140	0.00	-0.735	0.200	0.090	1.282	0.106
			DXS8103	0.068	0.32	0.099	0.00	-0.826	0.193	0.086	1.263	0.110
	>= 65	16	DXS984	0.017	0.42			-0.943	0.002	-0.001	-1.133	0.874
			DXS8106					-0.853	0.003	-0.001	-1.481	0.940
			DXS6806	0.000	0.50	0.000	0.50	-0.856	0.003	-0.001	-1.837	0.978
			DXS1200	0.820	0.00	0.820	0.00	0.442	0.747	0.463	-0.168	0.544
			DXS297	0.063	0.16	0.110	0.00	0.430	0.748	0.456	-0.047	0.497
			DXS1193	0.199	0.06	0.199	0.06	0.011	0.500	0.107	-0.515	0.681
			DXS8069	0.051	0.24	0.051	0.24	-0.300	0.203	0.004	-0.550	0.696
			DXS8103	0.173	0.14	0.173	0.14	-0.280	0.210	0.004	-0.517	0.682
	>= 65, 5+	7	DXS984	0.000	0.50	0.000	0.50	-0.772	0.000	-0.000	-1.294	0.903
			DXS8106	0.000	0.50	0.000	0.50	-0.598	0.001	-0.000	-0.778	0.743
			DXS6806	0.000	0.50	0.000	0.50	-0.545	0.001	-0.000	-0.680	0.712
			DXS1200	1.018	0.00	1.018	0.00	0.817	0.999	0.817	1.394	0.091
			DXS297	0.501	0.00	0.501	0.00	0.823	0.999	0.822	1.439	0.085
			DXS1193	0.123	0.00	0.123	0.00	0.349	0.996	0.348	0.588	0.262
			DXS8069	0.008	0.26	0.008	0.26	-0.021	0.496	0.012	0.297	0.336
			DXS8103	0.021	0.24	0.021	0.24	-0.034	0.494	0.004	0.304	0.336

APPENDIX J. *CAPB* RESULTS SUBSTRATIFIED BY MEDIAN AGE AT DIAGNOSIS AND NUMBER OF AFFECTED MEN

TABLE J-1. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *CAPB*, MEDIAN AGE

Group	Number of affected men	Number of Families	Marker	2-point lod	2-point θ	Multipoint Hold	Multipoint θ	Multipoint lod	Multipoint α	Multipoint hlod	Npl	p-value
Median Age < 6	5+	4	D1S1597	0.000	0.50	0.000	0.50	-1.591	0.000	-0.000	-0.353	0.606
			D1S407	0.013	0.28	0.013	0.28	-1.273	0.000	-0.000	-0.330	0.595
Median Age 60-64	5+	12	D1S1597	1.215	0.02	1.285	0.00	0.534	0.645	0.696	1.410	0.087
			D1S407	0.331	0.16	0.331	0.16	0.367	0.592	0.583	1.456	0.082
Median Age 65-69	5+	20	D1S1597	0.020	0.44	0.020	0.44	-3.829	0.000	-0.000	-0.194	0.544
			D1S407	0.202	0.22	0.346	0.00	-2.992	0.000	-0.000	-0.088	0.501
Median Age 70+	5+	11	D1S1597	0.000	0.50	0.000	0.50	-0.396	0.016	-0.002	0.293	0.354
			D1S407	0.000	0.50	0.000	0.50	-0.287	0.060	-0.004	0.456	0.299

TABLE J-2. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *CAPB*, TUMOR GRADE

Group	Median age, Number of affected men	Number of Families	Marker	2-point lod	2-point θ	Multipoint Hold	Multipoint θ	Multipoint lod	Multipoint α	Multipoint hlod	Npl	p-value
Low & Moderate Grade	< 65	11	D1S1597	0.000	0.50	0.000	0.50	-1.472	0.000	-0.000	-0.035	0.498
			D1S407	0.196	0.04	0.196	0.04	-1.223	0.000	-0.000	-0.136	0.538
	< 65, 5+	2	D1S1597	0.000	0.50	0.000	0.50	-1.045	0.000	-0.000	-0.208	0.475
			D1S407	0.286	0.00	0.286	0.00	-0.681	0.000	-0.000	-0.064	0.458
	>= 65	38	D1S1597	0.000	0.50	0.000	0.50	-1.546	0.001	0.001	0.361	0.348
			D1S407	0.122	0.22	0.122	0.20	-1.038	0.006	0.003	0.531	0.289
	>= 65, 5+	8	D1S1597	0.000	0.50	0.000	0.50	-1.243	0.000	-0.000	-0.477	0.650
			D1S407	0.064	0.24	0.081	0.04	-0.659	0.001	-0.000	-0.179	0.524
Moderate Grade Only	< 65	26	D1S1597	0.386	0.14	0.479	0.00	-0.475	0.398	0.378	0.764	0.217
			D1S407	0.383	0.12	0.383	0.12	-0.396	0.392	0.336	0.729	0.227
	< 65, 5+	7	D1S1597	0.443	0.10	0.512	0.00	-0.441	0.298	0.150	0.600	0.243
			D1S407	0.011	0.42	0.011	0.42	-0.724	0.201	0.068	0.405	0.301
	>= 65	31	D1S1597	0.022	0.42	0.022	0.42	-4.033	0.000	-0.000	-0.261	0.588
			D1S407	0.008	0.38	0.114	0.00	-3.647	0.000	-0.000	-0.227	0.575
	>= 65, 5+	13	D1S1597	0.024	0.42	0.024	0.42	-3.221	0.000	-0.000	-0.425	0.635
			D1S407	0.054	0.26	0.157	0.00	-2.777	0.000	-0.000	-0.387	0.620
At least 1 High-grade	< 65	10	D1S1597	0.454	0.06	0.466	0.00	0.430	0.925	0.428	1.091	0.132
			D1S407	0.268	0.16	0.268	0.16	0.500	0.971	0.497	1.285	0.102
	< 65, 5+	7	D1S1597	0.707	0.00	0.707	0.00	0.430	0.925	0.428	1.091	0.132
			D1S407	0.400	0.10	0.400	0.10	0.500	0.971	0.497	1.285	0.102
	>= 65	27	D1S1597	0.055	0.22	0.068	0.00	0.018	0.502	0.272	1.306	0.099
			D1S407	0.000	0.50	0.000	0.50	-0.153	0.488	0.218	1.224	0.113
	>= 65, 5+	10	D1S1597	0.004	0.38	0.004	0.38	0.239	0.833	0.239	0.944	0.164
			D1S407	0.000	0.50	0.000	0.00	0.157	0.671	0.186	0.956	0.162

TABLE J-3. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *CAPB*, CANCER STAGE

Group	Median age, Number of affected men	Number of Families	Marker	2-point lod	2-point θ	2-point Hold	2-point θ	Multipoint lod	Multipoint α	Multipoint hlod	Npl	p-value
Local Stage Only	< 65	21	D1S1597	0.000	0.50	0.000	0.50	-1.776	0.114	0.011	0.734	0.226
			D1S407	0.529	0.00	0.529	0.00	-0.973	0.207	0.046	0.811	0.205
	< 65, 5+	4	D1S1597	0.000	0.50	0.000	0.50	-1.627	0.000	-0.000	-0.429	0.592
			D1S407	0.000	0.50	0.000	0.50	-1.156	0.000	-0.000	-0.355	0.560
	>= 65	42	D1S1597	0.000	0.50	0.000	0.50	-2.026	0.005	0.003	0.670	0.247
			D1S407	0.000	0.44	0.000	0.44	-1.655	0.010	0.004	0.829	0.201
	>= 65, 5+	8	D1S1597	0.000	0.50	0.000	0.50	-1.151	0.001	-0.000	0.565	0.260
			D1S407	0.106	0.16	0.106	0.16	-0.557	0.026	-0.002	0.859	0.186
Local & Regional Stage	< 65	17	D1S1597	0.144	0.18	0.144	0.18	-0.562	0.265	0.077	0.193	0.408
			D1S407	0.035	0.30	0.035	0.30	-0.597	0.247	0.062	0.219	0.398
	< 65, 5+	6	D1S1597	0.512	0.04	0.512	0.04	-0.026	0.464	0.152	0.570	0.263
			D1S407	0.007	0.36	0.007	0.36	-0.090	0.417	0.117	0.613	0.251
	>= 65	38	D1S1597	0.151	0.26	0.151	0.26	-1.998	0.046	-0.005	0.554	0.279
			D1S407	0.082	0.26	0.155	0.00	-1.535	0.163	0.017	0.496	0.299
	>= 65, 5+	17	D1S1597	0.047	0.38	0.047	0.38	-2.247	0.000	-0.000	-0.094	0.265
			D1S407	0.072	0.26	0.144	0.00	-1.715	0.005	-0.001	0.013	0.243
At least 1 Distant Stage	< 65	9	D1S1597	0.810	0.02	0.817	0.00	0.576	0.927	0.573	1.300	0.096
			D1S407	0.619	0.08	0.619	0.08	0.204	0.566	0.340	1.137	0.121
	< 65, 5+	6	D1S1597	0.826	0.02	0.831	0.00	0.597	0.962	0.595	1.487	0.074
			D1S407	0.679	0.06	0.679	0.06	0.341	0.671	0.414	1.466	0.076
	>= 65	16	D1S1597	0.000	0.50	0.000	0.50	-1.535	0.000	-0.000	-0.050	0.497
			D1S407	0.011	0.32	0.090	0.00	-1.649	0.000	-0.000	-0.015	0.483
	>= 65, 5+	6	D1S1597	0.000	0.50	0.000	0.50	-0.826	0.000	-0.000	-0.451	0.621
			D1S407	0.000	0.50	0.024	0.00	-1.006	0.000	-0.000	-0.557	0.664

TABLE J-4. SUBSTRATIFIED ANALYSIS OF WHITE FAMILIES AT *CAPB*, AGGRESSIVE DISEASE

Group	Median age, Number of affected men	Number of Families	Marker	2-point lod	2-point θ	Hold	θ	Multipoint lod	Multipoint α	Multipoint hlod	Npl	p-value
No cases aggressive disease	< 65	19	D1S1597	0.000	0.50	0.000	0.50	-1.893	0.078	0.002	0.469	0.309
			D1S407	0.523	0.00	0.523	0.00	-1.057	0.175	0.032	0.579	0.273
	< 65, 5+	3	D1S1597	0.000	0.50	0.000	0.50	-1.718	0.000	-0.000	-0.722	0.735
			D1S407	0.000	0.50	0.000	0.50	-1.214	0.000	-0.000	-0.560	0.646
	>= 65	34	D1S1597	0.000	0.50	0.000	0.50	-1.953	0.001	-0.001	0.144	0.431
			D1S407	0.000	0.44	0.000	0.44	-1.537	0.002	-0.001	0.330	0.360
	>= 65, 5+	6	D1S1597	0.000	0.50	0.000	0.50	-1.398	0.000	-0.000	-0.141	0.500
			D1S407	0.075	0.18	0.075	0.18	-0.857	0.000	-0.000	0.143	0.396
Less than half cases aggressive disease	< 65	16	D1S1597	0.473	0.02	0.493	0.00	-0.353	0.175	0.004	0.157	0.416
			D1S407	0.000	0.50	0.000	0.50	-0.958	0.007	-0.002	-0.095	0.517
	< 65, 5+	6	D1S1597	0.819	0.00	0.819	0.00	-0.043	0.448	0.046	0.200	0.367
			D1S407	0.000	0.50	0.000	0.50	-0.555	0.019	-0.002	-0.076	0.477
	>= 65	43	D1S1597	0.037	0.40	0.037	0.40	-1.799	0.171	0.033	1.224	0.112
			D1S407	0.206	0.22	0.374	0.00	-1.473	0.275	0.109	1.256	0.107
	>= 65, 5+	18	D1S1597	0.023	0.44	0.023	0.44	-2.299	0.000	-0.000	0.368	0.327
			D1S407	0.129	0.24	0.272	0.00	-1.904	0.005	-0.002	0.450	0.299
Half or more cases aggressive disease	< 65	10	D1S1597	0.598	0.08	0.598	0.08	0.485	0.640	0.628	1.554	0.068
			D1S407	0.948	0.04	0.948	0.04	0.649	0.733	0.718	1.701	0.053
	< 65, 5+	6	D1S1597	0.836	0.04	0.836	0.04	0.705	0.822	0.721	1.867	0.046
			D1S407	1.179	0.00	1.179	0.00	0.863	0.974	0.861	2.094	0.033
	>= 65	16	D1S1597	0.000	0.50	0.000	0.50	-1.807	0.000	-0.000	-0.300	0.601
			D1S407	0.000	0.50	0.000	0.50	-1.830	0.000	-0.000	-0.409	0.644
	>= 65, 5+	7	D1S1597	0.000	0.50	0.000	0.50	-0.527	0.002	-0.000	-0.421	0.626
			D1S407	0.000	0.50	0.000	0.50	-0.518	0.002	-0.000	-0.432	0.631

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INVITED SPEAKER

"Conducting a Family Study: Prostate Cancer Linkage Analysis as an Example" *Interdisciplinary Club*, Fred Hutchinson Cancer Resarch Center, Seattle, WA, January 14, 2000.

"Genetic Epidemiology of Prostate Cancer: The Role of *HPC1* in High-Risk Prostate Cancer Families" *Interdisciplinary Training Grant Research Symposium*, Fred Hutchinson Cancer Resarch Center, Seattle, WA, October 8, 1999.

"Linkage Analysis at 1q24-25 in High-Risk Prostate Cancer Families: The Role of the Susceptibility Gene *HPC1*," *Program in Prostate Cancer Research Seminar*, Fred Hutchinson Cancer Resarch Center, Seattle, WA, February 5, 1999.

"Analysis of the Region Containing a Prostate Cancer Susceptibility Gene, *HPC1*, in 127 High-Risk Families," Genetic Susceptibility to Cancer Spotlight Session, *Society for Epidemiologic Research Annual Meeting*, Chicago, IL, June 24, 1998.

"Issues of Equity and Access in Biotechnology," *Student Pugwash National Conference*, Stanford University, Stanford, CA, January 27, 1995.

"Issues of Equity, Access, and Payment When Recruiting Patients/Subjects for Genetic Testing or Gene Therapy Research," "Policy Development and Ethical Pathfinding in Genetic Testing Services and Research: Ownership of Genetic Information," "A Human Genome Project Status Report: Scientific Developments and Ethical Issues in Cystic Fibrosis Testing and Research," *Conference on the Ethical Implications of the New Genetics*, Tufts University School of Medicine and Public Responsibility in Medicine and Research (PRIM&R), Boston, MA, May 5-6, 1994.

"Science Policy Analysis at the Congressional Office of Technology Assessment," *Alumni Career Panel*, Department of Biological Sciences and the University Career Center, Cornell University, Ithaca, NY, February 15, 1994.

"Summary of OTA Assessments Biomedical Ethics in U.S. Public Policy and The Human Genome Project and Patenting Human DNA Sequences," *Meeting of the NIH/DOE Joint Working Group on Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project*, Bethesda, MD, May 10, 1993.

POSTER PRESENTATIONS

Goode E.L., Stanford J.L., Gibbs M., Chakrabarti L., McIndoe R.A., Kolb S, Miller E.L., Hood L., Ostrander E.A., and Jarvik G.P., "*HPC1* Linkage Analysis and Consideration of Clinical Characteristics in High-Risk Prostate Cancer Families," Presentation in Genetic Susceptibility Poster Session, *Keystone Symposium "Molecular Epidemiology: A New Tool in Cancer Prevention,"* Taos, NM, February 10-15, 2000.

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Goode E.L., Kamineni A., Rudolph R., "Risk Factors for Gastrointestinal Anomalies and Abdominal Wall Defects," Presentation in Perinatal Poster Session, *Third Annual Washington State Joint Conference on Health*, Washington State Department of Health, Tacoma, WA, September 30-October 2, 1996.

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