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Genetics

Mendelian inheritance of familial prostate cancer

(segregation analysis/genetic epidemiology/autosomal dominant inheritance)

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ABSTRACT **Previous studies have demonstrated familial clustering of prostate cancer. To define the nature of this familial aggregation and to assess whether Mendelian inheritance can explain prostate cancer clustering, proportional hazards and segregation analyses were performed on 691 families ascertained through a single prostate cancer proband. The proportional hazards analyses revealed that two factors, early age at onset of disease in the proband and multiple affected family members, were important determinants of risk of prostate cancer in these families. Furthermore, segregation analyses revealed that this clustering can be best explained by autosomal dominant inheritance of a rare (q = 0.0030) high-risk allele leading to an early onset of prostate cancer. The estimated cumulative risk of prostate cancer for carriers revealed that the allele was highly penetrant: by age 85, 88% of carriers compared to only 5% of noncarriers are projected to be affected with prostate cancer. The best fitting autosomal dominant model further suggested that this inherited form of prostate cancer accounts for a significant proportion of early onset disease but overall is responsible for a small proportion of prostate cancer occurrence (9% by age 85). These data provide evidence that prostate cancer is inherited in Mendelian fashion in a subset of families and provide a foundation for gene mapping studies of heritable prostate cancer. Characterization of genes involved in inherited prostate cancer could provide important insight into the development of this disease in general.**

Molecular approaches to the understanding of human neoplastic disease have revealed that multiple genetic alterations are an essential component of tumorigenesis (1, 2). Both inherited and somatic genetic alterations can be involved in the malignant transformation of normal cells (3). Identification of the genes involved in neoplastic transformation has been approached through the molecular analysis of sporadic cancers and the genetic study of families with an inherited predisposition for cancer. The interplay of these two approaches has led to the characterization of genes such as the retinoblastoma gene, the p53 gene, and the *APC* gene that are each involved in the development of both hereditary and nonhereditary forms of cancer (4–15). Because inherited and noninherited cancers can share common genetic lesions, the study of inherited cancer syndromes can provide insights into understanding the development of cancer in general.

Prostate cancer is the most common cancer diagnosed and the second leading cause of cancer mortality in United States men (16). As with breast, colon, and other cancers for which Mendelian syndromes have been described and susceptibility genes have been mapped and cloned (14, 15, 17), family history is known to be a risk factor for prostate cancer (18–21), which raises the possibility that transmissible genetic factors may be involved in the development of this disease in a subset of men. The genetic contribution to diseases of complex origin such as cancer is often most salient in the families of early onset cases (22). Therefore, if prostate cancer is ever inherited in simple Mendelian fashion, it is most likely to be in the families with cases of earlier onset. In this study, Kaplan–Meier and Cox proportional hazards analyses were performed to assess whether there was clustering of prostate cancer in families of probands with early disease onset. In addition, a segregation analysis of 691 prostate cancer families was done to test the hypothesis of a Mendelian form of prostate cancer. Should such a Mendelian subtype of prostate cancer exist, it is a likely object for gene mapping studies and could serve as a useful model for understanding genetic alterations underlying prostatic tumorigenesis in general.

METHODS

Families. Families were ascertained through 740 consecutive probands undergoing radical prostatectomy for primary clinically localized prostate cancer at The Johns Hopkins Hospital, Baltimore, between 1982 and 1989. Cases were not selected for family history of disease. The mean age at onset of prostate cancer in these probands was 59.3 years (SD = 6.5 years). The median age at onset in the general population of U.S. Caucasian men diagnosed with prostate cancer is 73.5 years (23). The younger age at onset of the probands in this study reflects the fact that the cohort does not include men with metastatic disease or other age-related health problems that would preclude surgical intervention. Ninety-six percent of the probands were Caucasian; additional demographic characteristics of this sample are described elsewhere (18). In 1989, 691 probands were interviewed by telephone regarding family history of cancer. Probands were asked to recall cancer histories among fathers, brothers, uncles, and grandfathers. Positive family histories among first-degree relatives were validated in a sample of the reported cases by medical record review and found to be accurate (18). Negative family histories were not validated. Review of the family histories revealed that information was most complete on first-degree relatives (fathers and brothers) with substantial underreporting of prostate cancer among more distant relatives (18). Thus, only nuclear families are included in our analyses.

Proportional Hazards Analyses. Age-specific Kaplan–Meier estimates of cumulative prostate cancer risk were calculated for groups of relatives stratified by age at onset of disease in the family proband (<53 years, 53–65 years, and >65 years). These groupings allowed a comparison of risk in families of probands in the lowest quintile of age at onset (<53 years) to that of families of probands in the highest quintile (>65 years) of age at onset among these 691 probands. Differences in these Kaplan–Meier curves were assessed with the log-rank test. In addition, a Cox proportional hazards model was used to estimate hazard rates for probands'

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Abbreviation: df, degree(s) of freedom.

fathers and brothers. The dependent variable in the proportional hazards model was years to onset of prostate cancer in the probands' first-degree relatives. Independent variables tested included age at disease onset in the proband and an additional variable indicating whether each relative had any additional affected family members besides the proband. An interaction term between these two variables was also tested.

Segregation Analysis. To test specifically for Mendelian inheritance of prostate cancer in these families, regressive models were employed in a segregation analysis (24). These models represent an extension of conventional logistic regression wherein the phenotype of an individual is considered to be dependent on an unobserved "type" and other measured covariates. In such a model, type is a general term referring to discrete factors that influence a person's phenotype such as a Mendelian genotypes or environmental factors (25, 26). By constraining the parameters that describe the transmission of these types within families, one can specifically test the ability of genetic and nongenetic hypotheses to explain an observed phenotypic distribution in a set of family data.

In the present study, class A regressive models (24) as implemented in the REGTL module of the S.A.G.E. computer package (27) were used for analysis. The REGTL module permits segregation analysis of a truncated (censored) trait, such as age at onset of prostate cancer. Under this model, a proportion (γ) of the population with the potential to develop prostate cancer is deemed susceptible. As prostate cancer is sex-limited, γ was fixed at 0.0 for females in all analyses. Age at onset of prostate cancer is assumed to follow a logistic distribution described by two parameters, α and β, with the following probability distribution function: $f(\text{age}) = [\alpha e^{(\beta+\alpha*\text{age})}]/(1 + e^{(\beta+\alpha*\text{age})})^2$ (28). This symmetric distribution is similar to a normal distribution and has a mean, $-\beta/\alpha$, and variance, $\pi^2/3\alpha^2$. The cumulative distribution function is given by $F(\text{age}) = \gamma*\text{antilogit}(\beta + \alpha*\text{age})$ and represents the probability that a person will be affected by a given age.

Under the REGTL model used in the present analysis, the phenotype is the age at onset and the β parameter is type-dependent. This model allows the high-risk allele to influence the average age at onset for each type and, through this, the proportion of each type affected by a given age. In a common disease with late age at onset such as prostate cancer, low-risk individuals have a shifted age at onset distribution such that most will not be affected in the average lifetime. This model has been suggested (29) as appropriate for segregation analyses of common diseases with variable age of onset such as cancer.

The influence of genetic susceptibility was tested by considering three types of individuals (AA, AB, and BB) with three corresponding transmission parameters (τ_{AA}, τ_{AB}, and τ_{BB}) describing the probability of a parent of a given type transmitting the disease-producing factor A to offspring (30, 31). Under hypotheses of genetic transmission of disease, the τ parameters are constrained to Mendelian values of $\tau_{AA} = 1.0$, $\tau_{AB} = 0.5$, and $\tau_{BB} = 0.0$ that correspond to the probability that a parent of genotype AA, AB, and BB transmits the high-risk allele to their offspring, respectively. The model further assumes that the three types of parents (AA, AB, and BB) in these nuclear families occur in the population with frequencies q^2, $2q(1 - q)$, and $(1 - q)^2$.

Five models of disease transmission were tested against the general unrestricted model to identify the best model for these data. The "no major effect" or sporadic model assumes that baseline risk is not influenced by type; therefore, all persons have the same age-specific risk of prostate cancer. Mendelian models assume that a major locus with two alleles acting in codominant, dominant, or recessive fashion influences disease risk. An environmental model of nongenetically determined type-specific risk was also tested.

The best model was selected as the most parsimonious explanation for these family data that was not significantly different from the general unrestricted model. The likelihood ratio test was used to test each model against the general unrestricted model and was computed as minus twice the natural log likelihood ($-2 \ln L$) of the general model subtracted from that for a restricted model. This difference is distributed asymptotically as a χ^2 distribution with degrees of freedom equal to the difference in the number of parameters estimated in the two models. To obtain meaningful parameter estimates, ascertainment correction was performed by conditioning the likelihood of each pedigree on the proband's affection status by his age at examination (32, 33).

RESULTS

There were 119 affected men among the 1642 male first-degree relatives of the 691 prostate cancer probands. The mean age at onset of prostate cancer in these men was 70.5 years (SD = 10.4 years). Multiplex families included 1 affected father with 3 affected sons, 7 affected fathers with 2 affected sons, 4 sibships with 3 affected brothers, 11 sibships with 2 affected brothers, and 83 affected fathers with 1 affected son.

To assess whether there was variability in familial risk according to age at disease onset in the prostate cancer probands, Kaplan–Meier estimates of cumulative prostate cancer risk were calculated for probands' relatives in the three strata according to the age at onset of the proband (<52 years, 53–65 years, >65 years). Table 1 shows that relatives of younger cases had higher age-specific cumulative risks of developing prostate cancer compared to relatives of older cases. The hypothesis of no difference in time to onset of prostate cancer among relatives of probands in the three strata was clearly rejected by the log-rank test [$\chi^2 = 10.63$; degrees of freedom (df) = 2; $P = 0.0049$]. These data suggested stronger familial clustering among those with earlier onset of disease.

To further explore the hypothesis of familial clustering of early onset prostate cancer, a Cox proportional hazards model was employed to estimate hazard rates in the first-degree relatives of probands. The parameter estimates for the significant independent variables in the Cox proportional hazards regression are seen in Table 2. Multiple affected family members and earlier onset of disease in the proband were significant predictors of increased risk among the relatives. An interaction term between these variables was not

Table 1. Cumulative probability of prostate cancer in first-degree relatives of probands, by age of onset of prostate cancer in probands

Age of first-degree relatives, years	Cumulative probability, %		
	<53 years	53–65 years	>65 years
50–54	1.05 (0.74)	0.84 (0.32)	0.61 (0.43)
55–59	1.77 (1.03)	1.37 (0.41)	0.92 (0.53)
60–64	5.20 (1.96)	2.96 (0.66)	1.63 (0.72)
65–69	10.69 (3.02)	5.99 (1.05)	4.30 (1.29)
70–74	18.91 (4.47)	9.83 (1.49)	7.68 (1.94)
75–79	23.63 (5.31)	14.29 (1.98)	12.06 (2.84)
80–85	39.96 (9.29)	25.07 (3.21)	13.72 (3.23)

Probands were grouped by age at onset of prostate cancer (<53 years, 53–65 years, and >65 years). The log-rank test ($\chi^2 = 10.63$; df = 2; $P = 0.0049$) was used. Data are the mean; numbers in parentheses are the SEM. The numbers of first-degree relatives with prostate cancer are as follows: <53 years, 23; 53–65 years, 71; >65 years, 25. The numbers of first-degree relatives at risk are as follows: <53 years, 249; 53–65 years, 1006; >65 years, 387.

Table 2. Results for Cox proportional hazards analysis of prostate cancer in relatives of 691 prostate cancer probands

Variable	β	Standard error	P value
Age at onset (proband)	−0.0308	0.0107	0.0039
Family member besides proband affected	1.3386	0.2299	<0.0001

significant in a stepwise analysis, suggesting that these two factors are effectively independent.

Parameter estimates from the Cox proportional hazards analysis were used to calculate hazard ratios for relatives of probands with early disease onset and relatives with multiple affected family members. As seen in Table 3, an early age at onset of disease in the proband increased risk such that the relative of a proband diagnosed at age 50 was at 1.9-fold increased risk of prostate cancer compared to the relatives of a proband diagnosed at age 70. In addition, men with an additional affected relative (besides the proband) were at 4-fold higher risk of prostate cancer compared to those with no additional relatives affected. The combination of effects of early onset in the proband and multiple affected relatives was such that the relative of a proband diagnosed at age 50 with an additional relative affected was at 7-fold higher risk of prostate cancer compared to the relatives of a proband diagnosed at age 70 with no additional relatives affected.

The finding that relatives of men with early onset disease and with multiple affected family members had an increased risk of prostate cancer suggested a potential genetic etiology for the familial aggregation in these families. To assess whether this observed familial clustering of prostate cancer was consistent with Mendelian inheritance, a segregation analysis of prostate cancer in these families was performed. Parameter estimates and test statistics from the five models analyzed are shown in Table 4.

In comparison to the general unrestricted model, the two non-Mendelian models were clearly rejected. Specifically, the no major effect model with a single age at onset function and uniform risk to prostate cancer was rejected (model 1 vs. model 6; $\chi^2 = 30.2$; df = 6; $P < 0.001$). The environmental model was also rejected (model 5 vs. model 6; $\chi^2 = 26.4$; df = 4; $P < 0.001$), indicating that nongenetically determined type-specific risk did not explain the observed aggregation of prostate cancer.

Major gene models were tested by fixing the probabilities that homozygous susceptible, heterozygous, and homozygous normal (parameters τ_{AA}, τ_{AB}, and τ_{BB}) parents would transmit the high-risk allele to their offspring at 1.0, 0.5, and 0.0, respectively. The most general Mendelian model, a codominant model allowing for three genotype-specific age at onset distributions of prostate cancer, fits the data very well with a likelihood almost identical to that of the general unrestricted model (model 2 vs. model 6; $\chi^2 = 0.07$; df = 3; $P = 0.98$).

Table 3. Estimated hazard ratios for prostate cancer in relatives of probands, by age at onset in proband and additional affected family members

Age at onset of proband	Hazard ratio: No relatives	Hazard ratio: One or more relatives
50	1.9 (1.2–2.8)	7.1 (3.7–13.6)
60	1.4 (1.1–1.7)	5.2 (3.1–8.7)
70	1.0*	3.8 (2.4–6.0)

Hazard ratio by number of additional affected family members, besides proband, is shown. The numbers in parentheses are the 95% confidence interval.
*Reference group.

Testing of dominant and recessive Mendelian models against the general unrestricted models and the codominant Mendelian model allowed the mode of inheritance to be determined. The recessive model was clearly rejected when compared to the general unrestricted model (model 4 vs. model 6; $\chi^2 = 19.6$; df = 4; $P < 0.001$) and the codominant model (model 4 vs. model 2; $\chi^2 = 19.5$; df = 1; $P < 0.001$). The hypothesis of a dominant disease-producing allele, however, was fully consistent with the distribution of prostate cancer in these families. The dominant model was defined by constraining homozygous and heterozygous carriers of the high-risk allele to have the same age-specific risk of prostate cancer that was higher than the risk for noncarriers ($\beta_{AA} = \beta_{AB} > \beta_{BB}$). Comparison with the general unrestricted model revealed that the dominant model provided a good fit to these data (model 3 vs. model 6; $\chi^2 = 3.10$; df = 4; $P = 0.55$). Direct comparison of the dominant and codominant models showed that the codominant model did not provide a significant improvement in fit over the dominant model and that the dominant Mendelian model provided the best overall explanation for these data (model 3 vs. model 2; $\chi^2 = 3.03$; df = 1; $P = 0.08$).

Because the proportional hazards analysis suggested heterogeneity in familial risk according to the proband's age at onset, a test for etiologic heterogeneity among the three previously defined subsets of families (proband's age at onset: <53 years, 53–65 years, and >65 years) was performed. Heterogeneity was assessed by comparing for the best-fitting autosomal dominant model, the sum of the −2 ln L values obtained from separate analyses of each of the strata and the −2 ln L value obtained from the entire group of families (34). As seen in Table 5, the log likelihoods summed over the three strata were not significantly different from the log likelihood of the entire group providing no evidence for heterogeneity.

Parameter estimates from the best-fitting autosomal dominant model were used to calculate genotype-specific penetrances. In both homozygous (AA) and heterozygous (AB) carriers, the high-risk allele was very penetrant (88% by age 85), whereas the cumulative risk for noncarriers (BB) was

Table 4. Parameter estimates from segregation analysis of prostate cancer in 691 families ascertained through a single prostate cancer proband

Hypothesis	Model	−2 ln L	df	χ^2	P	Value of parameter: q	τ_{AA}	τ_{AB}	τ_{BB}	β_{AA}	β_{AB}	β_{BB}	α	γ
No major gene	1	1425.47	6	30.2	<0.001	[1.00]	—	—	—	−11.59	−11.59	−11.59	0.14	0.39
Codominant	2	1395.27	3	0.07	0.99	0.0027	[1]	[0.5]	[0]	−8.29	−13.74	−18.83	0.19	1.00
Dominant	3	1398.30	4	3.1	0.55	0.0030	[1]	[0.5]	[0]	−12.97	−12.97	−17.92	0.18	1.00
Recessive	4	1414.83	4	19.6	<0.001	0.3400	[1]	[0.5]	[0]	−12.24	−15.96	−15.96	0.16	0.80
Environmental	5	1421.70	4	26.4	<0.001	0.1400	0.14	0.14	0.14	−13.87	−12.76	−17.53	0.18	1.00
General	6	1395.20	—	—	—	0.0027	0.39	0.52	0.00	−8.19	−13.72	−18.79	0.18	1.00

χ^2 is defined as (−2 ln L) of the data under the hypothesis minus (−2 ln L) of the data under the general model. Numbers in brackets are the fixed initial value.

Table 5. Test for heterogeneity under the dominant model in three strata of families, by age of onset in the proband

Relatives of proband	(−2 ln L) of dominant model
Proband age (years)	
<53	253.7 (6)
53–65	932.8 (6)
>65	198.8 (6)
Total	1384.7 (18)
All relatives	1398.3 (6)
Difference	13.6 (12)
P value	0.33

Numbers in parentheses are the df.

much lower (5% by age 85). The estimated allele frequencies and the age-specific cumulative risks of disease for the three genotypes were used to calculate the relative proportion of prostate cancer cases in the population attributable to effects of the high-risk allele at various ages. Of the cumulative total prostate cancer cases occurring by ages 55, 70, and 85, this rare-high risk allele was responsible for 43%, 34%, and 9% of the cases occurring by these ages, respectively. Thus, there was an overall decline in the cumulative proportion of prostate cancer attributable to Mendelian inheritance with increasing age.

DISCUSSION

This report provides evidence that familial clustering of prostate cancer may be attributed to autosomal dominant inheritance of a rare yet highly penetrant high-risk allele. Proportional hazards analyses revealed that two factors (i.e., early age at onset of disease in the proband and multiple affected family members) were important determinants of risk of prostate cancer in these families. Segregation analysis employing models that allowed for a variable age at onset confirmed this finding and provided evidence for the Mendelian inheritance of prostate cancer. A model of autosomal dominant inheritance of a rare allele that predisposed carriers to be affected at earlier ages and in higher proportions than noncarriers gave the best fit to these families. This model suggested that the inherited form of the prostate cancer accounts for a significant proportion (43%) of early-onset disease (disease onset ≤55 years). However, this apparently inherited form of prostate cancer represents only a small proportion (9% by age 85) of all prostate cancer occurrence. Notably, only 2% of prostate cancer in U.S. Caucasian men occurs in those aged less than 55 whereas 90% of all cases occur in men aged less than 85 (23). Thus, the impact of hereditary prostate cancer in the population is the greatest at the younger ages that account for only a small proportion of the total disease occurrence. Despite the fact that only a small proportion of prostate cancer appears to be inherited in Mendelian fashion, genetic characterization of this subset of prostate cancer should provide significant insights into the molecular genetic mechanisms underlying prostatic tumorigenesis in general.

To our knowledge, this is the first report to describe a segregation analysis of prostate cancer and to report an autosomal dominant mode of inheritance of this cancer in a subset of families. Though we are unable to compare these results directly with other segregation analyses of prostate cancer, it should be noted that the findings of this study are similar to previous genetic analyses of other common adult onset tumors, especially breast cancer. Recent analysis of family data from the large Cancer and Steroid Hormone Study reinforces earlier findings that early age at onset and multiple affected family members are important risk factors for breast cancer (35). Segregation analyses of these data have indicated that a rare autosomal dominant gene present in the population with frequencies ranging from 0.0006 to 0.0033 may account for breast cancer in 4 to 6% of women (36, 37). Furthermore, carriers of the putative high-risk allele were estimated to have an earlier onset of breast cancer than noncarriers (37).

As described by Knudson (3, 38), the relationship between hereditary and nonhereditary forms of cancer provides a useful model for understanding prostatic tumorigenesis. Knudson's model suggests a class of genes, tumor suppressor genes, which may be involved in the development of hereditary and nonhereditary forms of cancer. According to Knudson's two-hit hypothesis used to explain the incidence of embryonic tumors (e.g., retinoblastoma and Wilms tumor), inactivation of both alleles at a tumor suppressor locus with the resultant loss of expression of its normal gene product permits the cell to override normal growth controls and leads to the development of cancer. In hereditary forms of cancer such as hereditary retinoblastoma, a mutated copy of one allele is inherited in the germ line; subsequent inactivation of the other allele in somatic cells leads to the development of cancer. Nonhereditary forms of cancer may occur as both of these hits occur at the level of the somatic cell. Knudson's original hypothesis has been borne out by the characterization of the retinoblastoma gene and its alterations in hereditary and nonhereditary retinoblastoma. Furthermore, the demonstration that germ-line mutations (12, 13) in the p53 tumor suppressor gene can lead to the development of the cancers of the Li–Fraumeni syndrome extends the relevance of Knudson's tumor suppressor model to inherited forms of adult-onset tumors. Tumor suppressor gene inactivation has been noted in sporadic prostate cancer (39) and may represent a mechanism of development of hereditary forms of the disease as well.

Genetic linkage studies to map specific genes involved in prostate cancer are a logical outgrowth of the present analysis. This work highlights the characteristics of families necessary for linkage studies of prostate cancer. Families with multiple affected members and early onset of disease are most likely to have a Mendelian form of prostate cancer appropriate for linkage analysis. Studies of genetic alterations in the DNA of primary human prostate cancers have revealed candidate genomic regions for these linkage studies. Allelic loss, a hallmark of tumor suppressor genes, has been noted to occur frequently in sporadic prostate tumors at chromosomes 16q, 10q, and 8p (40, 41). The potential relationship between inherited and noninherited forms of prostate cancer at the molecular level suggests that genomic regions identified by loss of heterozygosity in sporadic prostate cancer may serve as useful starting points for mapping genes involved in Mendelian forms of the disease.

This study was unable to fully address the issue of age and race heterogeneity because of its limited sampling frame. Within this younger group of predominantly Caucasian prostate cancer probands, the proportional hazards analysis suggested heterogeneity of familial risk according to the age at onset of the disease in the proband; however, there was no evidence for heterogeneity when the segregation analysis was similarly stratified by proband age at onset. Failure to detect such heterogeneity may have been due to poor statistical power, especially given the relatively narrow age range of probands in this study. Future studies that include more pedigree information from older men and Black men may be able to address more completely potential age- and race-related heterogeneity in prostate cancer inheritance.

In summary, here we have provided evidence for a form of prostate cancer that is inherited in autosomal dominant fashion. This analysis provides the logical framework for efforts to map the genes involved in this subset of a common cancer. The identification of genetic alterations in inherited

forms of this disease may serve as a useful biological model for understanding prostate cancer in general.

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