Am. J. Hum. Genet. 62:1425–1438, 1998

Evidence for Autosomal Dominant Inheritance of Prostate Cancer

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Summary

A family-history cancer survey was conducted on 5,486 men who underwent a radical prostatectomy, for clinically localized prostate cancer, in the Department of Urology at the Mayo Clinic during 1966–95; 4,288 men responded to the survey. Complex segregation analysis was performed to assess the genetic basis of age at diagnosis and the familial clustering of prostate cancer. For the total group, no single-gene model of inheritance clearly explained familial clustering of disease, which could be partly explained by lack of Hardy-Weinberg equilibrium, with an excess of homozygotes. After accounting for deviations from Hardy-Weinberg equilibrium, the best-fitting model that explained the familial aggregation and age at diagnosis was a rare autosomal dominant susceptibility gene, and this model fitted best when probands were diagnosed at <60 years of age. The model predicts that the frequency of the susceptibility gene in the population is .006 and that the risk of prostate cancer by age 85 years is 89% among carriers of the gene and 3% among noncarriers. A strength of our study is its large size, such that genetic models could be fitted within strata defined by the age of the proband. Although the autosomal dominant model was consistently the best model, the parameter estimates differed somewhat ($P = .03$) across the different age groups, suggesting genetic heterogeneity. Additional evidence that the hereditary basis of prostate cancer is likely to be genetically complex was provided by the following: (1) there was a significantly elevated age-adjusted risk of prostate cancer among brothers of probands, compared with their fathers (relative risk 1.5 [95% confidence interval 1.4–1.7]); (2) the autosomal dominant model predicted an excess of homozygotes, over that predicted by Hardy-Weinberg equilibrium; and (3) the model-predicted risk of prostate cancer among relatives was inadequate when probands were diagnosed at age $\geqslant 70$ years.

Received October 17, 1997; accepted for publication March 20, 1998; electronically published April 24, 1998.

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0002-9297/98/6206-0020$02.00

Introduction

Prostate cancer is the second most common malignant cancer among men living in the United States, after skin cancer. It is estimated that in 1997 ~334,500 new prostate cancer cases and ~41,800 prostate cancer–related deaths occurred in the United States (Parker et al. 1997) and that a man has a $\frac{1}{5}$ chance of developing prostate cancer during his lifetime (Feuer 1997). Age is the primary risk factor, with incidence per 100,000 increasing from 34 to 150 to 440 for U.S. Caucasian men ages 60, 70, and 80 years, respectively (Kosary et al. 1995). Cultural and ethnic background may also have an etiologic role, since there is a large variation in age-adjusted incidence in different racial/ethnic groups throughout the world, with the highest rates in U.S. African American men, followed by U.S. Caucasian men, and with the lowest rates among men in China and Japan (Muir et al. 1987). Although some of these population differences may be attributable to differences in diet and life style, there is strong evidence that genetic alterations, both somatic and heritable, play a major role in prostate cancer etiology.

A large number of studies have reported that male first-degree relatives (father, sons, and brothers) of an affected man are two to three times more likely to develop prostate cancer, compared with men in the general population (Woolf 1960; Cannon et al. 1982; Meikle and Stanish 1982; Carter et al. 1990; Steinberg et al. 1990; Spitz et al. 1991; Goldgar et al. 1994; Whittemore et al. 1995). A recent population-based case-control study reported an odds ratio of 2.5, after adjustment for age and ethnicity. Of most interest, however, is that this odds ratio did not significantly differ across the three U.S. and Canadian ethnic groups—African Americans, Caucasians, and Asian Americans (Whittemore et al. 1995)—despite the large difference in incidence among these ethnic groups. When there are multiple affected men in a family, the risk to the remaining men increases dramatically (Steinberg et al. 1990). A large twin study in Sweden reported the heritability of prostate cancer to be 33%–36% (Ahlbom et al. 1997).

To determine whether the familial clustering of prostate cancer was consistent with Mendelian inheritance, Carter et al. (1992) performed complex segregation analyses on 691 families ascertained through probands

undergoing radical prostatectomy for primary clinically localized prostate cancer. The model that best fitted their data was segregation of a rare autosomal dominant prostate cancer–susceptibility gene; the estimated frequency of the high-risk allele was 0.3%, and the estimated cumulative risk of prostate cancer by age 85 years was 88% for carriers, versus 5% for noncarriers. A second study employing complex segregation analysis of prostate cancer recently has reported results on a population-based sample of 2,857 Swedish nuclear families in which the father was diagnosed during 1959–63 (Grönberg et al. 1997*a*). This study confirmed that autosomal dominance best fitted the familial clustering of prostate cancer, but with a higher frequency of the susceptibility allele (1.67%) and a lower lifetime penetrance (63%).

The limitations of the study by Carter et al. (1992) are as follows: (1) the probands were primarily Caucasians (96%), which limited assessment of genetic heterogeneity across different ethnic groups; (2) the probands tended to be young (mean age at onset was 59.3 years, versus 73.5 years as the median age at diagnosis among U.S. Caucasian men), so that there was limited power to assess heterogeneity of autosomal dominant Mendelian transmission across different age groups, with a scarcity of men with later-onset disease; and (3) the study was conducted during 1982–89—that is, for the most part, before the 1987 introduction of serum prostate-specific antigen (PSA) testing to the community medical practice, making it difficult to extrapolate, to current clinical practice, hereditary prostate cancer diagnosed without use of PSA. The recent dramatic increase in prostate cancer incidence may be partly explained by the increased use of serum PSA testing (Jacobsen et al. 1995), leading to detection of early-stage cancers.

Further support for a genetic basis of prostate cancer is the finding of early age at onset and autosomal dominant inheritance within some families (Carter et al. 1993), as well as recent reports of genetic linkage of the disease, in ~34% of high-risk families, to chromosomal region 1q24-25 (Smith et al. 1996; Cooney et al. 1997), although this linkage finding has been difficult to reproduce consistently (McIndoe et al. 1997). Despite this evidence of autosomal dominant inheritance, others have reported findings that prostate cancer may have an X-linked or recessive genetic component (Monroe et al. 1995). The purposes of the present study were to determine whether results from complex segregation analyses, particularly Mendelian autosomal dominant inheritance, could be reproduced in an independent cohort of families and to assess heterogeneity due to age at diagnosis of the proband.

Methods

All men undergoing radical prostatectomy for clinically localized prostate cancer, in the Department of Urology at the Mayo Clinic (Rochester, MN), are registered in our database, which began to prospectively register men in 1987; cases from 1966–86 were retrospectively included. This cohort represents consecutive pathologically confirmed prostate cancer cases, without any selection other than that they were treated by a radical prostatectomy at the Mayo Clinic. A survey regarding family history of cancer and with detailed emphasis on prostate cancer, approved by our institutional review board, was sent in March 1995 to all 5,486 men who were registered in our database and alive at the time of the mailing; 866 deceased men were excluded. A second mailing was sent, in June 1995, to 1,434 men who had failed to return the first survey. The survey collected information on all sons, brothers, father, grandfathers, uncles, and male cousins, with regard to prostate cancer, and on any other cancers among other relatives. Age at diagnosis of prostate cancer was determined for all first-degree male relatives, as were vital status and either current age or age at death. Adoption status was also determined, to confirm biologic relationships. Prostate cancer history has been found to be accurately reported for first-degree relatives and to be underreported among more-distant relatives (Steinberg et al. 1990), which is similar to findings for other types of cancers (Bondy et al. 1994; Love et al. 1985). Because of these prior reliability studies, we did not validate family histories by medical-record review of relatives but, instead, restricted complex segregation analyses to first-degree relatives. However, all probands were treated at the Mayo Clinic and had thorough medical examinations. If a proband reported that he was adopted, then only his sons were included in the segregation analyses.

Complex segregation analyses were performed by use of genetic regressive models (Bonney 1986,) as implemented in the SAGE (1994) computer package. Two general factors, labeled "A" and "B," were considered, and these are assumed to give rise to three "types" of people, labeled "AA," "AB," and "BB." Under a genetic model, these three types represent the genotypes for two alleles, A, and B. For nongenetic models, these three types are arbitrary, but they allow for population heterogeneity that is not necessarily due to genetic differences. Genetic contributions to the model are incorporated into the transmission parameters τ_{AA}, τ_{AB}, and τ_{BB}, the probability that persons of a given type transmit the A factor to their offspring (Elston and Stewart 1971; Lalouel et al. 1983). Mendelian models of transmission restrict the transmission parameters to $\tau_{AA} = 1$, $\tau_{AB} = .5$, and $\tau_{BB} = 0$, but more-general models provide the

ability to test whether transmission fits Mendelian expectation. Furthermore, the population frequencies of the three types of founding parents in the pedigrees are represented by P_{AA}, P_{AB}, and P_{BB}. These frequencies are restricted to sum to 1, and, when Hardy-Weinberg equilibrium (HWE) is assumed, these three frequencies depend on the population frequency, q, of allele A ($P_{AA} = q^2$, $P_{AB} = 2q[1 - q]$, and $P_{BB} = [1 - q]^2$).

The SAGE REGTL module was used to analyze age at diagnosis while allowing for censored observations (any male relative who did not have prostate cancer at either his current age or the time of his death). Note that age at diagnosis differs from age at onset, because diagnosis depends on both the natural history of prostate cancer and the methods used for diagnosis. Age at diagnosis, denoted as "x," was assumed to be distributed according to a logistic distribution (Bonney 1986), which has the probability-distribution function $P(x) = [\gamma\alpha e^{(\beta+\ \alpha x)}]/[1 + e^{(\beta+\alpha x)}]^2$ and the cumulative distribution function $F(x) = \gamma[e^{(\beta+\alpha x)}]/[1 + e^{(\beta+\alpha x)}]$. According to this model, the parameter α determines the rate of change in the probability of prostate cancer as it depends on age, and hence α determines the variability in the age at diagnosis; we assumed that α is the same for all three types of people. The parameter β influences the mean age at diagnosis (mean $-\beta/\alpha$), and this parameter was allowed to depend on the type of person (the genotype of the person, for the genetic models). The parameter γ is the "susceptibility" parameter, the cumulative probability that one will have prostate cancer if he or she lives long enough (Go et al. 1983); for all models, γ was fixed to be 0 for females. To correct for the method of ascertainment, the likelihood for each pedigree was conditioned on the proband's disease status at his age at diagnosis.

Complex segregation analyses were performed by fitting four Mendelian models (dominant, recessive, codominant, and additive) and three non-Mendelian models (a general unrestricted model; an environmental model without generation effects, for which there is no transmission of disease and for which the risk of prostate cancer is assumed to be the same for both parent and child generations [$\tau = q$], although the three types were allowed to differ in disease probability, in order to allow for population heterogeneity; and an environmental model with generation effects, which is similar to an environmental model without generation effects but allows for generation differences [$\tau \neq q$]). Hypotheses of disease transmission were tested by subtraction of twice the $\log_e$ likelihood of a restricted model from twice the $\log_e$ likelihood of the general unrestricted model. This difference was compared with a χ^2 distribution with df conservatively estimated as the difference in the number of estimated parameters for the two models compared.

Comparison of participants versus nonparticipants, as well as comparison of positive and negative family history, were made by use of χ^2 statistics for categorical variables and by the Wilcoxon rank-sum test for age at diagnosis. The cumulative distribution of prostate cancer among first-degree relatives was estimated by Kaplan-Meier methodology, accounting for censored observations. These distributions were correlated with characteristics of the proband, by use of log-rank statistics, and relative risks were estimated by the Cox proportional-hazards model.

Results

Characteristics of Probands

Family-history questionnaires were sent to 5,486 men, 4,288 (78%) of whom were used for segregation analyses. The reasons for exclusion of 1,198 men were as follows: failure to return the questionnaire, return of blank questionnaires, or refusal to participate, (n = 1,134); proband deceased, without a proxy relative to complete the questionnaire (n = 43); being lost to follow-up (n = 4); and proband adopted and without a son (n = 17). The clinical characteristics of the participant and nonparticipant probands differed statistically, for a number of factors (table 1), but the large sample size allowed detection of some minor clinical differences. The most striking difference was a higher rate of recurrence among nonparticipants, which may be due to less willingness to participate by those men more ill because of their disease (table 1). Among the 4,288 participants, the clinical characteristics were similar for the 1,214 probands (28% of total) who had at least one first-degree relative with prostate cancer and the 3,074 probands (72% of total) without an affected first-degree relative (table 2).

Correlation of Proband's Characteristics with Relative's Age at Diagnosis

A total of 17,684 male relatives were reported on the survey; they included 4,224 fathers (637 affected, 828 with unknown status, and 2,759 without prostate cancer), 6,789 brothers (863 affected, 604 of unknown status, and 5,322 without prostate cancer), and 6,671 sons (17 affected, 156 of unknown status, and 6,498 without prostate cancer). Relatives were scored as having an unknown status for prostate cancer if the proband either indicated an unknown status for his relative or left this response blank. The clinical characteristics of each proband were analyzed to assess whether any were correlated with the age at diagnosis among his relatives. The age at diagnosis of the proband was trichotomized by the cutoffs of 60 and 70 years, which approximately

Table 1

Clinical Characteristics, by Survey Participation

Characteristic	No. (%) of Participants (n = 4,288)	No. (%) of Nonparticipants (n = 1,198)	P
TNM pathological stage:[a]			
$T_0N_0M_0$	30 (.7)	17 (1.4)	.001
$T_1N_0M_0$	101 (2.4)	21 (1.8)	
$T_2N_0M_0$	1,764 (41.4)	439 (37.1)	
$T_{34}N_0M_0$	1,814 (42.6)	517 (43.7)	
$T_xN_1M_0$	550 (12.9)	188 (15.9)	
$T_xN_xM_1$	0 (0)	1 (.1)	
Unknown	29	15	
Pathological grade:			
1	82 (2.0)	24 (2.1)	.61
2	2,304 (54.7)	637 (55.0)	
3	1,677 (39.8)	447 (38.6)	
4	150 (3.6)	50 (4.3)	
Unknown	75	40	
Recurrence:			
Local	251 (5.9)	102 (8.5)	.001
Systemic	153 (3.6)	91 (7.6)	.001
Method at diagnosis:			
Needle biopsy	3,890 (90.7)	1,096 (91.6)	.34
Transurethral resection	288 (6.7)	78 (6.5)	
Other	110 (2.6)	24 (1.8)	
Age at diagnosis (years):			
Median	65.6	66.4	.0005
Range	38–84	41–81	

[a] T_0 = no evidence of primary tumor; T_1 = clinically undetectable tumor; T_2 = tumor confined within prostate; T_{34} = tumor extended throughout prostatic capsule; T_x = tumor unable to be assessed; N_0 = no regional lymph-node metastasis; N_1 = metastasis in single lymph node, $\leqslant$2 cm; N_x = regional lymph nodes unable to be assessed; M_0 = no distinct metastatis; and M_1 = distant metastatis.

correspond to the 20th and 80th percentiles of the distribution. Earlier age at diagnosis for the proband was significantly correlated with an earlier age at diagnosis among his first-degree relatives (fig. 1), but no other clinical characteristics of the proband were correlated with the distribution of the age at diagnosis among first-degree relatives (table 3).

Segregation Analyses

The results from fitting segregation models when HWE was assumed are presented in table 4. All environmental and single-gene models were clearly rejected as having adequate fits, relative to the general model. Among the genetic models, the codominant model fitted best, followed by the recessive model. To assess the lack of model fit, all seven models were fit without restriction to HWE (table 5). All models except the environmental model without generation effects demonstrated significant evidence against HWE (table 5). Although a substantial improvement in fit of the models was achieved, with the best-fitting model as autosomal dominant, no single model adequately explained the familial clustering of prostate cancer.

To evaluate additional sources of heterogeneity, we split the data into three subsets based on the age at diagnosis of the proband (<60, 60–69, and $\geqslant$70 years) and determined the best fit for the seven models, but not assuming HWE. For each subset, the best-fitting model was a rare autosomal dominant model (tables 6–8). However, only for the subset of probands diagnosed at age <60 years (table 6) did the autosomal dominant model give an adequate fit, one that was much better than that of the autosomal recessive model. For the later-diagnosed probands (tables 7 and 8), the difference between dominant and recessive inheritance was not as clear, even though the dominant model had a better fit; the fit of the dominant model was not adequate for probands diagnosed at age 60–69 years (table 7) and was marginally adequate for probands diagnosed at age $\geqslant$70 years (table 8). The estimated parameters for the dominant models did not differ substantially across the three age subsets, although a formal test of heterogeneity across these subsets indicates that heterogeneity may exist (χ^2 = 23.09, df = 12, P = .03). As shown in figure 2, the estimated age-dependent penetrances are similar for the subset defined by proband age at diagnosis <60 years and for the subset defined by age at diagnosis 60–69 years, whereas the subset defined by proband age at diagnosis $\geqslant$70 years tended to have a shift toward a

Table 2

Clinical Characteristics of Participating Probands With and Without a Family History of Prostate Cancer among First-Degree Relatives

Characteristic	Family-History Status: Negative (n = 3,074)	Family-History Status: Positive (n = 1,214)	P
TNM pathological stage:[a]			
$T_0N_0M_0$	24 (.8)	6 (.5)	.50
$T_1N_0M_0$	70 (2.3)	31 (2.6)	
$T_2N_0M_0$	1,248 (40.9)	516 (42.8)	
$T_{34}N_0M_0$	1,304 (42.7)	510 (42.3)	
$T_xN_1M_0$	406 (13.3)	144 (11.9)	
Unknown	22	7	
Pathological grade:			
1	61 (2.0)	21 (1.8)	.16
2	1,623 (53.8)	681 (57.0)	
3	1,218 (40.4)	459 (38.4)	
4	116 (3.8)	34 (2.9)	
Unknown	56	19	
Recurrence:			
Local	174 (5.7)	77 (6.3)	.39
Systemic	113 (3.7)	40 (3.3)	.54
Age at diagnosis (years):			
Median	65.5	65.7	.95
Range	38-84	44-80	

For definitions, see footnote to table 2.

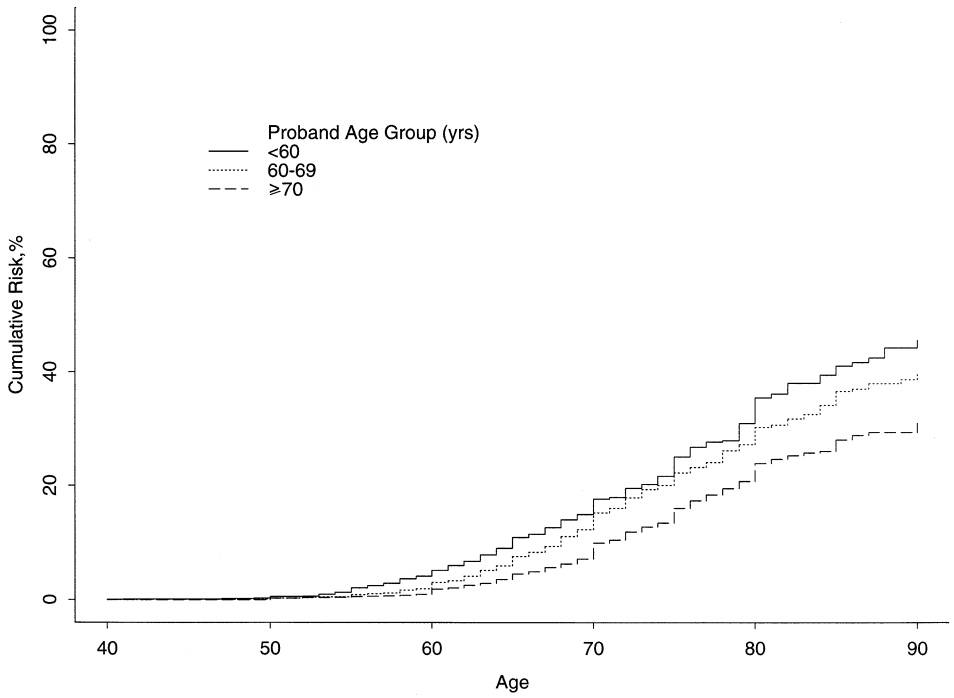

Figure 1 Cumulative risk of prostate cancer among first-degree relatives, according to age at diagnosis of the proband. Cumulative risks were estimated by nonparametric Kaplan-Meier methodology.

higher age at onset, both for carriers and for noncarriers. This could be due to a higher frequency of sporadic cases among the families with older probands.

To compare the predicted and observed cumulative risks of prostate cancer among the fathers and brothers of probands, the empirical cumulative risks were estimated separately for fathers and brothers, for each of the three strata defined by the probands' age at diagnosis: <60 years, 60–69 years, and ⩾70 years. These cumulative risks are presented in figures 3–5. When adjustment is made for the age strata of the proband, the risk to brothers was significantly greater than the risk to fathers ($P = .0001$), with a relative risk of 1.5 (95% confidence interval 1.4–1.7). Based on the parameters of the autosomal dominant model that are given in table 5, the predicted cumulative risk to first-degree relatives is also presented in figures 3–5. This predicted risk is conditional on the age at diagnosis of the proband, as defined by the strata. For probands diagnosed at age <70 years, the predicted risks were between the empirical risk for fathers and that for brothers (figs. 3 and 4), suggesting that the model predictions were accurate. However, for probands diagnosed at age ⩾70 years, the predicted risk grossly underestimated the observed risk (fig. 5); this is mainly because it was assumed that the age at diagnosis of the proband was 70–85 years for the predicted risk, whereas our actual data had few probands diagnosed at age >80 years. If we restricted the age of proband's diagnosis to 70 years, then the predicted risk (not shown) agreed closely with the observed risk shown in figure 5. Hence, the prediction error in figure 5 represents extrapolation beyond the limits of our data. In addition to use of the autosomal dominant model, for the total data set (table 5), to predict risk to relatives, each of the autosomal dominant models fitted to the three age strata (tables 6–8) were used to predict risk, but these predictions (not shown) were close to those presented in figures 3–5.

For the autosomal dominant model, HWE was strongly rejected for each age category (HWE models not shown; $P < .0001$). The cause of deviation from HWE could be due to a stratified sample, such that allele frequencies and disease prevalence differ across different ethnic subgroups, and mating is not random between the different ethnic subgroups. Our sample of probands is neither population based nor homogeneous with respect to ethnic background; rather, this sample is based on referrals to the Mayo Clinic, a tertiary-care center, with 3,826 probands representing 49 states of the United States (excluding Hawaii) and Washington, DC, and with 462 probands from outside the United States. A total of 1,051 probands were Minnesota residents at the time of their surgery; this subset is more homogeneous with respect to ethnic background than is the total of

Table 3

Correlation of Proband's Characteristics with Age-Adjusted Relative Risk of Prostate Cancer among First-Degree Relatives

Characteristic of Proband	No. of Prostate Cancers	Age-Adjusted Relative Risk (Standard Error)[a]	*P*
Age at diagnosis (years):			
<60 (n = 3,062)	279	1.74 (.08)	.0001
60–69 (n = 7,985)	786	1.43 (.07)	
⩾70 (n = 3,163)	282	1.0[b]	
Pathological grade:			
1 (n = 231)	28	1.0[b]	.67
2 (n = 7,618)	754	.97 (.19)	
3 (n = 5,574)	500	.92 (.19)	
4 (n = 526)	42	.85 (.24)	
Unknown (n = 261)	23	.77 (.28)	
TNM pathological stage:[c]			
$T_0N_0M_0$ (n = 108)	4	.29 (.52)	.12
$T_1N_0M_0$ (n = 369)	40	1.0[b]	
$T_2N_0M_0$ (n = 5,827)	566	.99 (.16)	
$T_{34}N_0M_0$ (n = 5,873)	558	1.01 (.16)	
$T_xN_1M_0$ (n = 1,938)	168	.89 (.18)	
Unknown (n = 95)	11	1.08 (.34)	
Ploidy status:			
Diploid (n = 8,394)	795	1.0[b]	.15
Aneuploid/tetraploid (n = 3,781)	357	.95 (.06)	
Unknown (n = 2,035)	195	.86 (.08)	

[a] Estimated by Cox proportional-hazards models.
[b] Reference group.
[c] For definitions, see footnote to table 1.

all probands. For this subset of Minnesota residents, we determined the best-fitting autosomal dominant models, with and without the restriction of HWE; HWE was rejected in this subset ($\chi^2 = 41.12$, $P < .001$), and the estimated parameters of the autosomal dominant model were similar for Minnesota residents and the total group. On the basis of this analysis, we could not find evidence that ethnic heterogeneity was the potential major source of deviation from HWE.

We have assumed that the age at diagnosis has a logistic probability distribution. Deviations from this assumed distribution could cause a lack of fit of the models. To assess this, we attempted to simultaneously estimate parameters that transform the age at diagnosis to better fit a logistic distribution (Box-Cox transformation), along with the other genetic model parameters. However, these attempts failed, because the numerical algorithms did not converge. As an alternative, we transformed the age at diagnosis by the natural logarithm and fitted the seven models, with and without HWE. These results (model-fit χ^2 values and P values) are presented at the bottoms of tables 4–8. Under HWE (table 4), the recessive model fitted somewhat better than the dominant model, but all genetic models fitted poorly. In contrast, when HWE was not required (tables 5–8), the dominant model fitted substantially better than the recessive model. We conclude that the lack of model fit is primarily due to lack of HWE and not to the choice of transformation for age. The restriction of HWE in our data forces an underestimate of the frequency of ho-

Table 4

Segregation Models Assuming HWE

	Mendelian Models				Environmental Models[a]		
	Dominant	Recessive	Additive	Codominant	Without Generation Effects	With Generation Effects	General Model
Parameter:							
q_A	.0079	.3323	.0053	.3738	.3296*	.2350	.0089
τ_{AA}	1.0[b]	1.0[b]	1.0[b]	1.0[b]	.3296*	.3486*	1.0
τ_{AB}	.5[b]	.5[b]	.5[b]	.5[b]	.3296*	.3486*	.832
τ_{BB}	.0[b]	.0[b]	.0[b]	.0[b]	.3296*	.3486*	.0072
β_{AA}	−13.60	−13.76	−7.95	−13.94	−21.62	−22.35	−11.83
β_{AB}	−13.60	−19.38	−14.06	−21.66	−15.52	−15.55	−14.29
β_{BB}	−19.32	−19.38	−20.17	−17.24	−18.25	−18.49	−19.84
α	.188	.190	.194	.193	.227	.228	.195
γ	1.0	1.0	1.0	1.0	.479	.487	1.0
$-2\ell n$ L	15,212.33	15,134.68	15,224.94	15,105.83	15,393.66	15,386.61	15,036.29
Model fit χ^2:	176.04	98.39	188.65	69.54	357.37	350.32	
df	4	4	4	3	3	2	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	
After $\log_e$ transformation:[c]							
Model fit χ^2:	189.70	117.37	195.96	105.37	400.45	381.16	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

[a] Within each column, parameters denoted by an asterisk (*) are constrained to be equal.
[b] Parameter is fixed at value shown.
[c] Parameter estimates after $\log_e$ transformation are not given.

Table 5

Segregation Models Not Requiring HWE

	Mendelian Models				Environmental Models[a]		
	Dominant	Recessive	Additive	Codominant	Without Generation Effects	With Generation Effects	General Model
Parameter:							
P_{AA}	.0036	.0659	.0450	.0038	.1709*	.4773	.0024
P_{AB}	.0051	.1844	.1654	.0051	.3896†	.2699	.0698
P_{BB}	.9914	.7496	.7895	.9911	.4395‡	.2527	.9064
τ_{AA}	1.0[b]	1.0[b]	1.0[b]	1.0[b]	.1709*	.1839*	1.0
τ_{AB}	.5[b]	.5[b]	.5[b]	.5[b]	.3896†	.1839*	.841
τ_{BB}	.0[b]	.0[b]	.0[b]	.0[b]	.4395‡	.1839*	.084
β_{AA}	−13.47	−13.64	−13.63	−13.34	−22.17	−20.27	−14.81
β_{AB}	−13.47	−19.47	−19.08	−13.47	−15.65	−15.67	−17.67
β_{BB}	−19.02	−19.47	−24.52	−18.95	−18.35	−17.82	−24.01
α	.183	.188	.188	.183	.231	.237	.229
γ	1.0	1.0	1.0	1.0	.504	.449	1.0
$-2\ell n$ L	15,050.63	15,104.62	15,139.91	15,049.99	15,392.86	15,324.76	15,005.59
Model fit χ^2:	45.04	99.03	134.32	44.40	387.27	319.17	
df	4	4	4	3	3	2	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	
Test of HWE χ^2 (1 df):	161.70	30.06	85.03	55.84	.80	68.90	30.70
P	<.0001	<.0001	<.0001	<.0001	.37	<.0001	<.0001
After $\log_e$ transformation:[c]							
Model fit χ^2	44.73	113.29	205.85	43.19	401.55	341.23	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

[a] Within each column, parameters with the same superscript symbol (*, †, or ‡) are constrained to be equal.
[b] Parameter is fixed at value shown.
[c] Parameter estimates after $\log_e$ transformation are not given.

mozygous carriers (.0001 for HWE vs. .0036 for non-HWE) and an overestimate of the frequency of heterozygous carriers (.0157 for HWE vs. .0051 for non-HWE). Also, without HWE (table 5), the general-model transmission parameters $\tau_{AB} = .841$ and $\tau_{BB} = .084$ are both greater than they should be for a genetic model (.5 and 0, respectively), which can occur when there are more affected offspring than are predicted by a genetic model. We have examined outlier pedigrees (defined as those having a large positive or negative additive contribution to the model χ^2); yet, after removal of the 16 most extreme pedigrees, the general-model transmission parameters were still larger than those for a genetic model. Phenocopies, a mixture of dominant and recessive effects, and secular trends in diagnosis could cause the lack of fit of these genetic parameters.

Discussion

Our results support the existence of a rare autosomal dominant prostate cancer–susceptibility gene that causes an earlier age at onset among carriers. Support for this finding is strongest among men diagnosed at age <60 years but is consistent among men diagnosed at older ages. Our results tend to indicate that hereditary prostate cancer is genetically complex and that a high rate of phenocopies at older ages may be a reason why an autosomal dominant model does not give a complete explanation of the familial clustering of this disease. This was particularly evidenced by the inadequacy of the best-fitting model to predict the cumulative risk of prostate cancer among first-degree relatives of men diagnosed at age $\geqslant$70 years. Although, on the basis of the age at diagnosis of the proband, there is some statistical evidence that heterogeneity of the autosomal dominant model may exist, the model parameters are similar for probands diagnosed at age <70 years. Probands diagnosed at age $\geqslant$70 years may have a higher frequency of nonhereditary prostate cancers among their relatives, but the best-fitting model in this subset was autosomal dominant, suggesting that the proband's age at diagnosis cannot be used to reliably discriminate hereditary from nonhereditary–prostate cancer families; rather, it is likely that the pattern of inheritance in a family (Carter et al. 1993), including the mean age at diagnosis, would be the better discriminant. Although the autosomal recessive model did not adequately fit our data, brothers of

Table 6

Segregation Models for Probands Diagnosed at Age <60 Years

	Mendelian Models				Environmental Models[a]		
	Dominant	Recessive	Additive	Codominant	Without Generation Effects	With Generation Effects	General Model
Parameter:							
P_{AA}	.0046	.0645	.1189	.0046	.1865*	.4453	.0041
P_{AB}	.0029	.1367	.3129	.0029	.3556†	.2367	.0050
P_{BB}	.9925	.7987	.5681	.9925	.4579‡	.3180	.9909
τ_{AA}	1.0[b]	1.0[b]	1.0[b]	1.0[b]	.1865*	.2022*	1.0
τ_{AB}	.5[b]	.5[b]	.5[b]	.5[b]	.3556†	.2022*	.2538
τ_{BB}	.0[b]	.0[b]	.0[b]	.0[b]	.4579‡	.2022*	.0
β_{AA}	−12.62	−12.11	−12.23	−12.61	−18.79	−21.14	−12.66
β_{AB}	−12.62	−18.18	−18.46	−12.61	−15.25	−15.90	−12.53
β_{BB}	−18.04	−18.18	−24.69	−18.03	−18.79	−18.99	−18.22
α	.173	.167	.168	.173	.238	.253	.173
γ	1.0	1.0	1.0	1.0	.498	.510	1.0
-2ℓn L	3,101.44	3,119.44	3,120.69	3,101.44	3,136.99	3,123.39	3,100.53
Model fit χ^2:	.91	18.91	20.16	.91	36.46	22.86	
df	4	4	4	3	3	2	
P	.923	.0008	.0005	.823	<.0001	<.0001	
After $\log_e$ transformation:[c]							
Model fit χ^2	13.34	32.61	33.52	13.07	51.42	43.79	
P	.010	<.0001	<.0001	.0045	<.0001	<.0001	

[a] Within each column, parameters with the same superscript symbol (*, †, or ‡) are constrained to be equal.
[b] Parameter is fixed at value shown.
[c] Parameter estimates after $\log_e$ transformation are not given.

Table 7

Segregation Models for Probands Diagnosed at Age 60–69 Years

	Mendelian Models				Environmental Models[a]		
	Dominant	Recessive	Additive	Codominant	Without Generation Effects	With Generation Effects	General Model
Parameter:							
P_{AA}	.0026	.1918	.1919	.0026	.2308*	.5473	.0779
P_{AB}	.0039	.8082	.8081	.0039	.4198†	.3111	.0923
P_{BB}	.9935	.0	.00	.9934	.3494‡	.1417	.8297
τ_{AA}	1.0[b]	1.0[b]	1.0[b]	1.0[b]	.2308*	.2412*	1.0
τ_{AB}	.5[b]	.5[b]	.5[b]	.5[b]	.4198†	.2412*	1.0
τ_{BB}	.0[b]	.0[b]	.0[b]	.0[b]	.3494‡	.2412*	.2089
β_{AA}	−14.12	−14.69	−14.69	−14.09	−23.96	−20.98	−15.92
β_{AB}	−14.12	−20.81	−20.79	−14.12	−16.74	−16.34	−19.81
β_{BB}	−19.76	−20.81	−26.89	−19.75	−19.84	−18.22	−26.28
α	.194	.203	.203	.194	.244	.242	.229
γ	1.0	1.0	1.0	1.0	.567	.483	1.0
-2ℓn L	8,644.14	8,671.77	8,672.12	8,644.13	8,808.69	8,752.02	8,603.44
Model fit χ^2:	40.70	68.33	68.68	40.69	205.25	148.58	
df	4	4	4	3	3	2	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	
After $\log_e$ transformation:[c]							
Model fit χ^2	29.08	65.48	65.11	28.76	203.31	148.01	
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

[a] Within each column, parameters with the same superscript symbol (*, †, or ‡) are constrained to be equal.
[b] Parameter is fixed at value shown.
[c] Parameter estimates after $\log_e$ transformation are not given.

Table 8

Segregation Models for Probands Diagnosed at Age ⩾70 Years

	Mendelian Models				Environmental Models[a]		
	Dominant	Recessive	Additive	Codominant	Without Generation Effects	With Generation Effects	General Model
Parameter:							
P_{AA}	.0017	.0570	.0343	.0019	.1689*	.3699	.0023
P_{AB}	.0045	.1379	.1304	.0045	.2312†	.1451	.0159
P_{BB}	.9938	.8050	.8353	.9935	.5999‡	.4849	.9817
τ_{AA}	1.0[b]	1.0[b]	1.0[b]	1.0[b]	.1689*	.0528*	1.0
τ_{AB}	.5[b]	.5[b]	.5[b]	.5[b]	.2312†	.0528*	.7495
τ_{BB}	.0[b]	.0[b]	.0[b]	.0[b]	.5999‡	.0528*	.0115
β_{AA}	−14.27	−14.20	−14.13	−13.89	−20.67	−20.09	−13.69
β_{AB}	−14.27	−20.32	−19.59	−14.29	−15.24	−15.01	−15.58
β_{BB}	−20.51	−20.32	−25.05	−20.39	−17.09	−17.36	−21.67
α	.191	.192	.191	.190	.223	.232	.209
γ	1.0	1.0	1.0	1.0	.404	.368	1.0
$-2\ell n$ L	3,281.96	3,287.33	3,303.47	3,280.05	3,378.62	3,368.47	3,273.03
Model fit χ^2:	8.93	14.30	30.44	7.02	105.59	95.44	
df	4	4	4	3	3	2	
P	.063	.006	<.0001	.071	<.0001	<.0001	
After $\log_e$ transformation:[c]							
Model fit χ^2	11.74	19.19	33.50	10.52	110.64	101.77	
P	.019	.0007	<.0001	.0146	<.0001	<.0001	

[a] Within each column, parameters with the same superscript symbol (*, †, or ‡) are constrained to be equal.
[b] Parameter is fixed at value shown.
[c] Parameter estimates after $\log_e$ transformation are not given.

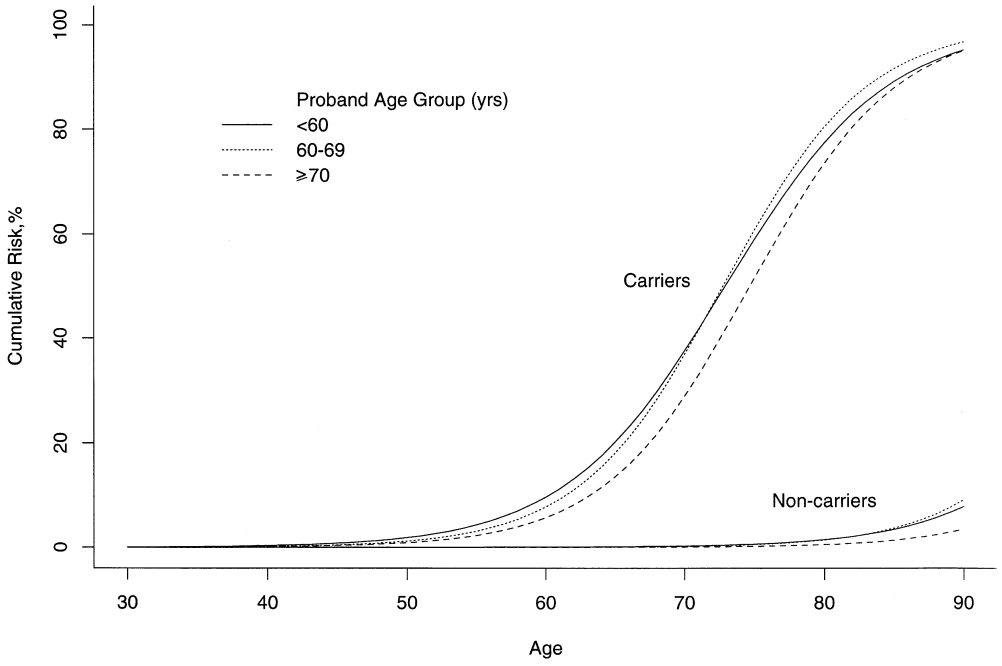

Figure 2 Predicted cumulative risk of prostate cancer for carriers and noncarriers, based on autosomal dominant models for subsets defined by age at diagnosis of the proband: <60, 60–69, and ⩾70 (70+) years.

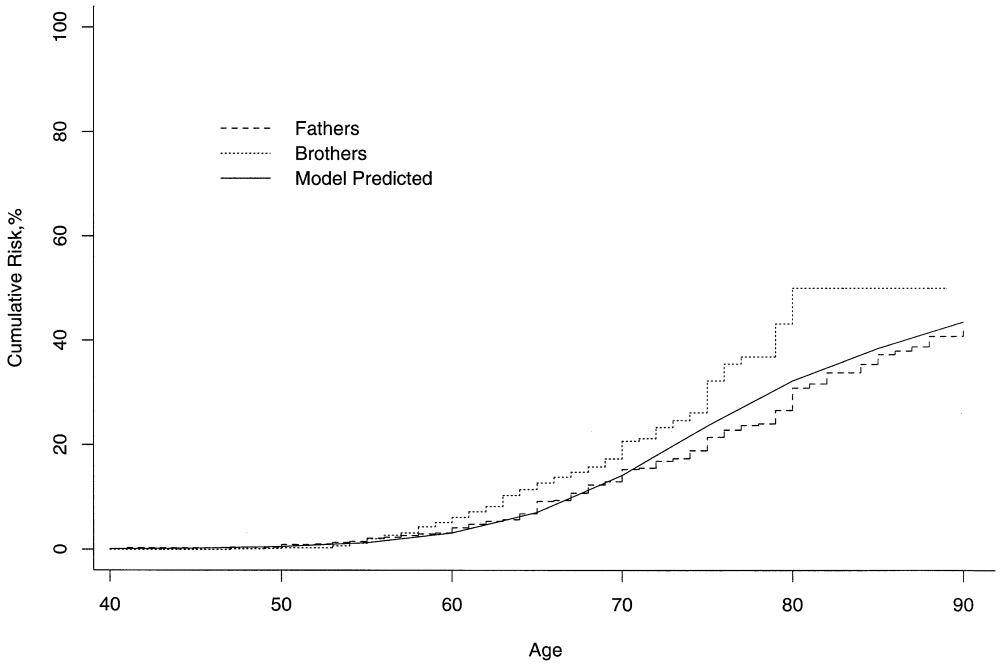

Figure 3 Cumulative risk of prostate cancer among fathers and brothers of probands who were diagnosed at age <60 years (Kaplan-Meier estimates), and predicted risk based on the autosomal dominant–model parameters given in table 5.

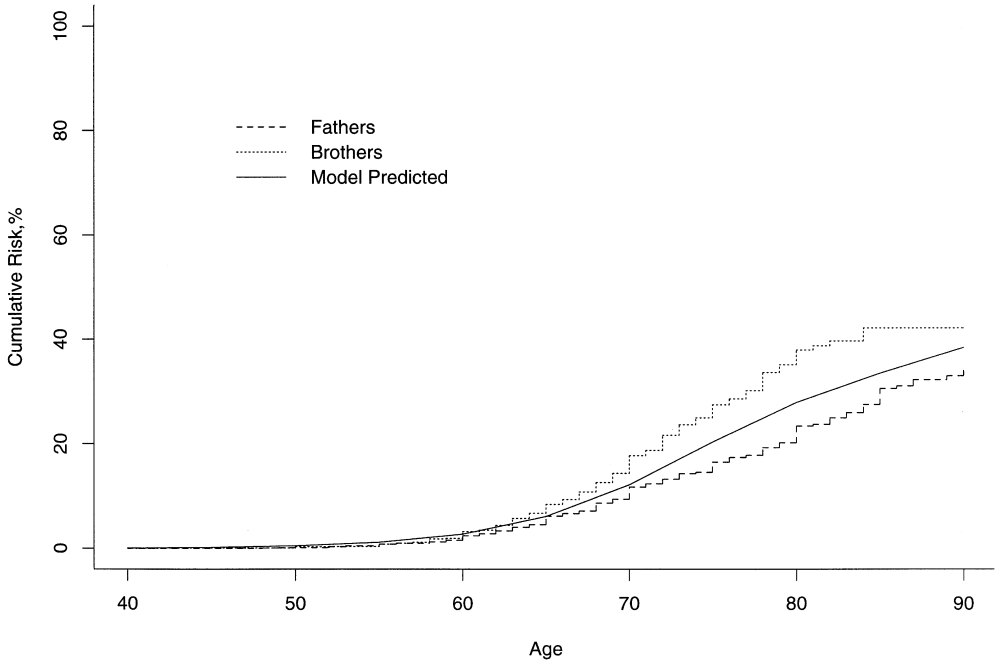

Figure 4 Cumulative risk of prostate cancer among fathers and brothers of probands who were diagnosed at age 60–69 years (Kaplan-Meier estimates), and predicted risk based on the autosomal dominant–model parameters given in table 5.

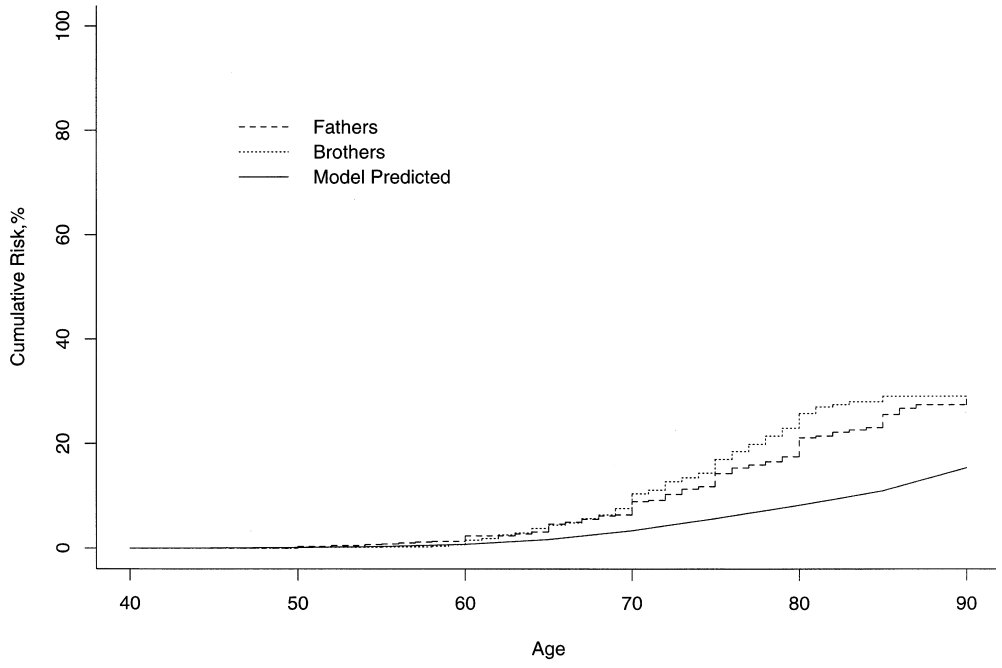

Figure 5 Cumulative risk of prostate cancer among fathers and brothers of probands who were diagnosed at age $\geqslant$70 years (Kaplan-Meier estimates), and predicted risk based on the autosomal dominant–model parameters given in table 5.

probands were at a higher risk of prostate cancer than were fathers of probands. These results are consistent with a recent report that found the prevalence of prostate cancer to be greater among men who have at least one brother affected, compared with men whose father is affected (Monroe et al. 1995). The authors of that report interpreted this to suggest that some prostate cancer may be explained by an X-linked or autosomal recessive component. However, underreporting among fathers, who, unlike brothers, were not likely to be diagnosed by PSA, could explain this finding. These issues, in conjunction with a significant lack of HWE proportions, implicate a complex genetic mechanism, with perhaps a mixture of autosomal dominant and recessive effects, as well as strong secular changes in the incidence of prostate cancer that are due to improved diagnostic procedures.

There are sources of potential biases that limit generalization of our findings to all prostate cancer. First, we selected men because they had undergone a radical prostatectomy. To be eligible for this surgery, a man could not have metastatic disease, nor could his general health be poor. This ascertainment could select against hereditary–prostate cancer families. Recent results by Grönberg et al. (1997*b*) suggest that men with prostate cancer in families demonstrating linkage to the hereditary prostate cancer 1 (HPC1) locus on chromosome 1q24-25 tend to have a younger age at diagnosis, higher-grade tumors, and more-advanced disease, compared with the general population of prostate cancer cases. Another potential bias was that 7.6% of the nonparticipants had systemic recurrence, compared with 3.6% of the participants, suggesting that some of the nonparticipants may have had a more aggressive disease. Although the quantitative implications of these potential biases are difficult to address, we suspect that they would weaken our power to detect Mendelian segregation of prostate cancer. Given that the Mendelian models gave much better fit than the environmental models, our results strongly support the existence of hereditary prostate cancer, with evidence favoring autosomal dominant segregation.

Carter et al. (1992) performed segregation analyses similar to those that we have presented here, using similar ascertainment—through probands receiving a radical prostatectomy for clinically localized prostate cancer at Johns Hopkins University (JHU)—and the same methods of analysis. It is encouraging that our findings are similar to those reported by Carter et al. (1992), albeit only after we adjust for lack of HWE. For their autosomal dominant model, under HWE, the estimated susceptibility-gene frequency was .003, whereas for our similar model (table 4) we estimated a gene frequency of .008. Not requiring HWE, we estimated the gene frequency as being .006. The estimated age-specific penetrances for the JHU and Mayo Clinic models are presented in figure 6. The estimated penetrances for carriers were similar, although, for noncarriers, the JHU model tended to have a greater cumulative incidence than was

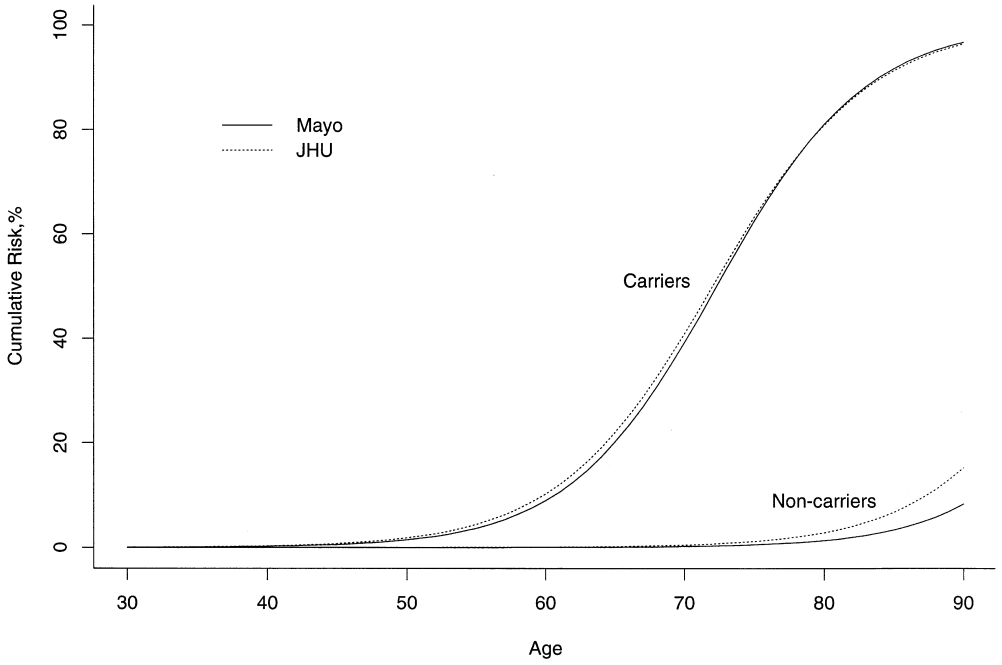

Figure 6 Comparison of the best-fitting dominant model, assuming HWE, between the Mayo Clinic data (Mayo) and the JHU data (Carter et al. 1992).

seen in our Mayo Clinic model. On the basis of SEER data (Kosary et al. 1995), one would expect a higher incidence of prostate cancer among noncarriers than would be predicted by our model. The low estimated lifetime penetrance among noncarriers could be due to underreporting, many relatives not screened by PSA (e.g., older brothers and fathers who died prior to the widespread use of PSA screening), or a combination of both. Although the assumption of HWE was not reasonable for our data, this assumption had little impact on the estimated cumulative-incidence curves.

The utility of our best-fitting dominant models (tables 5–8) derives from the fact that the model parameters can be used to specify the gene frequency (.006; see table 5) and age-specific penetrance for parametric linkage analysis. The recent report of a major prostate cancer–susceptibility locus on chromosome 1 (Smith et al. 1996) found a parametric two-point LOD score of 3.65 and a multipoint LOD score of 5.43, after allowance was made for linkage heterogeneity, with linkage to chromosome 1 in ~34% of the families. These parametric analyses were based on population-based segregation analyses in Swedish men (Grönberg et al. 1997*a*). For disease-gene mapping in families selected for early-onset disease, the parameters in table 6, for probands diagnosed at age <60 years, may offer a reasonable alternative model for parametric linkage analyses. However, misspecification of penetrance can dramatically diminish the power of genetic-linkage analyses, so it may be worthwhile to consider a few reasonable parametric models, as well as recent model-free methods (Kruglyak et al. 1996). We are currently scanning the genome by genetic markers, in search of prostate cancer–susceptibility genes. Our selection of families has focused on those with at least three living men affected with prostate cancer, with preference for brothers and/or cousins with an early age at onset.

Our crude analysis, comparing probands' characteristics versus status of family history for prostate cancer, did not reveal any clinical/pathological features that could be used to discriminate a genetic predisposition to prostate cancer. A more refined analysis, correlating the proband's characteristics with the age at diagnosis of his relative(s), indicated that only the proband's age at diagnosis correlated with his relative's age at diagnosis. However, the potential ascertainment biases, discussed above, could explain why the other clinical characteristics of the proband did not correlate with his relative's age at diagnosis. It would be of interest to determine whether pathological/clinical outcomes are correlated among affected relatives, because this may give insight into the biology of hereditary prostate cancer and would offer useful clinical information. However, we did not have pathological/clinical-outcome information on the

relatives, so we could not perform these types of analyses.

In summary, our results are consistent with previous reports that carriers of a prostate cancer–susceptibility gene have a much earlier age at onset, relative to noncarriers. This finding is consistent with data on other tumor-suppressor genes leading to cancer, such as the BRCA1 gene, which increases the risk of breast cancer (Easton et al. 1993). A potential limitation of both our study and that of Carter et al. (1992) is that probands were ascertained because they had undergone a radical prostatectomy. This led to the study of (*a*) men in whom the age at diagnosis was earlier than the national average and (*b*) primarily localized disease. Hence, our results may not be generalizable to all ages, although it is provocative that the subset analysis of probands diagnosed at age $\geqslant 70$ years indicated that the dominant model was the best fitting. Because of the high frequency of prostate cancer among elderly men, and because of the complexity of hereditary prostate cancer, collaborative efforts, such as the recently formed International Consortium on Prostate Cancer Genetics (Smigel 1997), will likely be needed to sort out the role of genetics in this disease.

Acknowledgments

The dedicated work by the following clerical staff, computer programmers, and study coordinators made this work possible: Amie Bissonett, Marcia Brumm, Karen Hanson, Judy Larson, Sandra Shirk, Amelia Stobaugh, and Holly Wieland. This work was supported in part by the U.S. Public Health Service, National Institutes of Health, grant R01 CA 72818. Some of the results reported herein were obtained by use of the program package SAGE, which is supported by U.S. Public Health Service resource grant 1 P41 RR03655 from the National Center for Research Resources.

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