Review

Inherited Genotype and Prostate Cancer Outcomes[1]

Timothy R. Rebbeck[2]

Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, and Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6021

Abstract

Prostate cancer is the most commonly diagnosed noncutaneous tumor in North American men and confers significant morbidity and mortality to the general population. The use of screening tools to detect prostate cancer at an early stage may have beneficial effects on an individual's prognosis. However, the intense use of these screening modalities also detects tumors that may have a relatively benign course and for which intensive treatment is not necessary. There is a large body of research that evaluated biochemical, physiological, or somatic genetic measures in relation to prostate cancer progression or prognosis. Environmental exposures may also affect these outcomes. In contrast, inherited markers of genetic susceptibility to prostate cancer have largely been used to predict occurrence of disease rather than disease outcome. The use of inherited genetic markers to evaluate prostate cancer outcome could enhance our ability to identify those men who are more likely to develop clinically significant prostate cancer and to intervene in these men to reduce morbidity and mortality resulting from prostate cancer.

Introduction

Prostate cancer remains the leading cause of cancer death in elderly men in the United States (1). Unlike most cancers, a sizeable proportion of prostate tumors may exist without producing symptoms (2–6). The prevalence of prostate cancer in autopsied men with no clinical evidence of disease ranged from 12% in men ages 40–49 to 43% in men >80 years. Although diagnoses of prostate cancer under the age of 50 are rare, prostate cancer is also present in younger men. Sakr *et al.* (7) studied 152 African-American and United States Caucasian men ages 10–49 and identified small foci of prostate cancer in 27% of men in their 30s and in 34% of men in their 40s. These results suggest that both clinically apparent and occult prostate cancers are common, even in young men.

The widespread use of screening for prostate cancer by serum PSA[3] and digital rectal examination has dramatically changed the pattern of prostate cancer incidence in the United States. Rates of prostate cancer incidence increased sharply from 1986 to 1993, apparently in part because of the detection of latent prostate tumors in the general population (1). Prostate cancer incidence rates have since fallen, but shifts to lower stage or grade tumors compared with those detected before the advent of PSA screening have persisted (1). A concern with this "stage shift" is whether a lead-time or length-time bias may be acting to provide an apparent benefit for screening, when in fact none exists.

Despite these concerns, overall survival in men who are diagnosed with prostate cancer at an early stage is significantly better than in men diagnosed later (8), making early detection important for some men. Although many prostate cancers that are detected by screening and are treated surgically have clinical significance to the patient (9, 10), even tumors with a potentially poor prognosis may not lead to significant morbidity or mortality, particularly in older men. Controversy therefore exists about what kind of treatment (if any) should be pursued in these cases (11). Unnecessary treatments may result in morbidity that could be avoided if tumors destined to take an indolent course could be identified. Because of these concerns, the ability to identify biomarkers that predict prostate cancer outcomes could serve an important role in the course of making clinical decisions when prostate cancer is diagnosed.

There is a large body of research that evaluates whether prostate cancer natural history or prognosis can be predicted by biochemical traits (*e.g.*, serum PSA levels), histopathological indices (*e.g.*, tumor grade and stage), or somatic genetic mutations. A number of prognostic models have been developed to predict probability of poor outcome in men with prostate cancer (12–14). However, relatively little information exists about whether inherited genotypes can be used to improve the ability to predict prostate cancer outcomes. Genotype information may affect disease outcome through at least two different means:

(*a*) Inherited genotype data may influence the natural history of disease by acting directly in tumor etiology. For example, inherited genotypes may influence tumor histopathology including the stage or grade of disease, the rate of disease progression, or the propensity for metastasis.

(*b*) Inherited genotype may influence an individual's response to either chemoprevention or the pharmacological treatment of disease. For example, inherited genotypes may influence the bioavailability of a chemopreventive or chemotherapeutic agent, or it may predict the occurrence of toxicities that may influence an individual's cumulative timing or dose of exposure. Some genes could conceivably affect both natural history and treatment response.

The purpose of this review is to summarize molecular

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[2] To whom requests for reprints should be addressed, at Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 904 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021. Phone: (215) 898-1793; Fax: (215) 573-2265; E-mail: trebbeck@cceb.med.upenn.edu.

[3] The abbreviations used are: PSA, prostate-specific antigen; AR, androgen receptor; VDR, vitamin D receptor; CYP, cytochrome P-450; TNM, Tumor-Node-Metastasis; TMPT, thiopurine methyltransferase.

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epidemiological studies that relate inherited genotype information to outcomes associated with a diagnosis of prostate cancer.

Genetics of Prostate Cancer Natural History and Prognosis

The role of somatic genetic mutations, including loss or amplification or specific genes in prostate tumors, has been correlated with the natural history of prostate cancer progression and therefore clinical prognosis [reviewed by Latil and Liderau (15) and Ozen and Pathak (16)]. Inherited (germ-line) mutations in candidate genes may be associated with disease prognosis if they are involved in metabolic events that lead to tumor progression. These events include regulation of somatic DNA damage or repair directly or via the metabolism of compounds that induce DNA damage and the metabolism of steroid hormones that induce the growth of prostate tumors. Therefore, some of the genes that may be considered candidates for prostate cancer initiation may also be candidates for prostate tumor progression and/or prognosis.

Hereditary Prostate Cancer Etiology

It has long been known that an excess of prostate cancer occurs in some families (17). Since the time that prostate cancer was recognized as a familial disease, complex segregation analyses have been undertaken that indicated that a rare, autosomal dominant gene segregates in a few families that have hereditary patterns of prostate cancer (18–20). This putative gene or genes confers a relatively high lifetime prostate cancer penetrance (*e.g.*, 63–89%, depending on the data set and model applied). However, the frequency of disease-causing alleles in the populations studies has been inferred to be only 0.3–0.6% in the United States and 1.7% in Scandinavia. These figures, and the estimates emanating from these analyses, suggest that only a small proportion (perhaps no more than 10%) of all prostate cancer occurs in men who carry a single gene mutation with an autosomal dominant pattern of inheritance. A number of loci have been identified that explain these hereditary patterns of prostate cancer [reviewed by Ostrander and Stanford (21)]. Only two genes, *RNASEL* and *HPC2/ELAC2*, have been isolated and may confer hereditary prostate cancer risk (22, 23), although the evidence supporting a role for *HPC2/ELAC2* is conflicting (24–27). The strongest evidence from genetic linkage analysis for an additional prostate cancer susceptibility gene is that of *HPC1* on chromosome 1q24–25 (28), and *RNASEL* (22) is located in this genomic region. However, this gene is likely to explain only a small proportion of hereditary prostate cancers. Additional linkage analyses have identified putative hereditary prostate cancer loci on chromosomes 1p36 (*CAPB*), 20q13 (*HPC20*), Xq27–28 (*HPCX*), and 1q42.2–q43 (*PCAP*). However, few of the reports of linkage at these loci have been confirmed in an independent report that gives strong evidence favoring the existence of the gene. Therefore, the genetics of hereditary prostate cancer remains unresolved.

Hereditary Prostate Cancer and Natural History or Progression

It is not yet clear whether prostate cancers with a hereditary component have a difference natural history or prognosis than those without a hereditary etiology. Rodriguez *et al.* (29) reported that men with a positive family history of prostate cancer have a poorer stage, grade, or prognosis than men who do not have a family history. Keetch *et al.* (30) reported a lower Gleason grade among men with a hereditary pattern of cancer compared with sporadic cases but no difference for any other tumor characteristic. In contrast, a number of reports (12, 19, 31–34) did not observe statistically significant differences in factors usually associated with prognosis including Gleason grade, tumor stage, and PSA at diagnosis between men with and without a family history of prostate cancer. Bova *et al.* (33) also reported no difference between hereditary and nonhereditary prostate cancer cases in maintaining an undetectable PSA after radical prostatectomy with 5-year follow-up. Although study design and statistical power issues may have contributed to these apparently inconsistent results, reports to date have not resolved whether or under what circumstances prostate tumors associated with inherited genotypes (known or inferred by family history) are associated with different natural history or prognosis.

The lack of overwhelming evidence for differences in hereditary *versus* nonhereditary prostate cancers may be explained by the complexity surrounding hereditary prostate cancer genetics in general. Thus, identification of genes that confer hereditary prostate cancer risk may help to identify population subsets in which the natural history of disease, and thus disease prognosis, may differ from other prostate cancer cases in the general population. Grönberg *et al.* (35) undertook a genetic linkage analysis of 74 hereditary prostate cancer families form North America and identified 33 (45%) that provided evidence for linkage to the *HPC1* locus. A comparison was made of prostate cancer characteristics in the linked *versus* unlinked families. Linked families had a significantly earlier mean age at prostate cancer diagnosis than unlinked families. Tumors in the linked families were of higher grade and advanced stage than in the unlinked families. There were no differences in PSA levels between the two groups of families. In contrast to the studies of hereditary prostate cancer not associated with a defined genetic etiology, these results suggest that *HPC1* confers not only susceptibility to develop prostate cancer but also a propensity for more aggressive disease. Goddard *et al.* (36) also found that detection of linkage to *HPC1* was enhanced when Gleason score was considered in the linkage model. These results suggest that *HPC1*-associated prostate cancers have a different natural history than non-*HPC1* cancers.

The studies described above considered the occurrence of prostate cancer as the primary outcome stratified cancer characteristics by those who may and may not have an *HPC1* mutation. In contrast, Witte *et al.* (37) undertook a genome-wide linkage analysis using a Gleason score as the analytical variable of interest to identify genes associated with prostate tumor aggressiveness. Using a sample of 513 brothers with prostate cancer, they undertook a genome-wide scan for genes associated with Gleason score. Those authors identified regions on chromosomes 5q, 7q, and 19q as containing putative prostate cancer "aggressiveness" genes. Although no gene has been isolated in these regions that could explain the authors' results, these findings represent an approach to identify those genes that may confer clinically significant disease in some families.

Genes and Nonhereditary Prostate Cancer Etiology

In contrast to the evidence for the existence of genes responsible for some hereditary occurrences of prostate cancer, molecular epidemiological studies have yet to provide consistent inferences about the role of low penetrance genes in prostate cancer etiology. There are a number of examples of low penetrance genes in prostate cancer etiology (reviewed in Ref. 38). These include genes involved in the metabolism of environmental carcinogens (*e.g.*, *CYP2D6*, *CYP2C19*, *GSTM1*,

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GSTP1, *GSTT1*, *NAT1*, and *NAT2*), those involved in androgen metabolism (*AR*, *CYP17*, and *SRD5A2*), and others including the vitamin D receptor (*VDR*) and *KLK3*, the gene encoding PSA. In addition, *HPC2* has also been suggested to confer prostate cancer risk outside of the context of hereditary prostate cancer in some but not all studies (24, 25, 27, 39, 40). In general, few consistent associations between any of these genes and prostate cancer risk have been identified. The majority of these studies have been undertaken in small sample sets, and rarely have there been confirmatory analyses using independent samples. Therefore, it is difficult to assess whether consistent and strong associations exist for any of the existing candidate genes of interest.

From the list of candidate genes, the *AR*, *CYP17*, *SRD5A2* (5α-reductase type II), and *VDR* genes have been studied most widely. Lengths of the *AR-CAG* and *AR-GGN* repeat polymorphisms have been reported in a number of studies to be associated with prostate cancer risk in some (41–45) but not all (46, 47) studies. Similarly, associations of *SRD5A2* have been reported by some groups (48, 49) but not others (50, 51). *CYP17* has been consistently reported to be associated with prostate cancer by a number of groups. However, the direction of the association for the same polymorphism has been reported to be positive in some studies (51–54) and inverse in one other (54). Finally, a number of polymorphisms in *VDR* exist and have been studied in association with prostate cancer risk. Some studies have shown no association of any *VDR* polymorphism and prostate cancer risk (55–58), whereas others have reported an association with one of many polymorphisms studied (42, 57), without a consistent replication with the same polymorphic variant in multiple studies. Therefore, although many of these genes may play a role in prostate cancer etiology, there remains relatively little information about which genes, which polymorphisms, and in which populations or population subsets these genes will exert their effects on prostate cancer risk.

Genes and Nonhereditary Prostate Cancer Natural History or Prognosis

There is limited evidence to date about the role of candidate genes as modulators of prostate cancer natural history or clinical outcome (Table 1). It is biologically plausible that genotypes involved in androgen metabolism could be associated with different tumor characteristics, if these genotypes modulated the bioavailability of androgens to prostate tumors. Genotypes that could plausibly have this effect include *CYP3A4*, *AR*, *CYP17*, and 5α-reductase II (*SRD5A2*). Similarly, it is plausible that genes involved in DNA damage (including genes associated with carcinogen metabolism) may affect tumor characteristics if they regulate the accumulation of somatic genetic damage in a tumor cell and are therefore associated with the progression of a tumor to a higher clinical stage or grade.

AR. Despite reports that shorter polyglutamine repeats in *AR*s are associated with tumor stage, grade, or survival (41–43, 49), a relationship of *AR* alleles and prostate cancer characteristics has not been seen in all studies. Three studies reported no strong relationship of *AR* polymorphism with higher tumor stage or grade (45–47). However, both Bratt *et al.* (47) and Edwards *et al.* (46) reported marginally significant associations of *AR* genotype and tumor stage or grade ($P = 0.07$ in both studies), suggesting that a relationship of *AR* and tumor severity may be found in a larger sample set. The population studied by Hsing *et al.* (45) consisted of men in China in whom prostate cancer screening was not common and for whom the distribution of tumors differed substantially from that of the other groups in that it had a much higher proportion of advanced disease. Another difference lies in the source of study subjects. The subjects studied by Giovannucci *et al.* (41) were drawn from large cohorts of men; the subjects studied by Ingles *et al.* (42), Stanford *et al.* (43), Hsing *et al.* (45), and Bratt *et al.* (47) were drawn from population-based studies; and the sample of Edwards *et al.* (46) was a hospital-based study. Differences in the nature of the study samples may explain some of the apparent discrepancy in results across studies.

Nam *et al.* (49) reported no overall association of short *AR*-CAG repeat length with survival, but that in low grade and stage cancers (*i.e.*, those with generally favorable prognosis), the recurrence risk was 8-fold higher in men with shorter *AR*-CAG repeats than in men with longer repeats. In contrast, Bratt *et al.* (47) reported that cases with longer CAG repeats responded better to endocrine therapy, even after adjusting for PSA, tumor grade, and tumor stage. Although there is some evidence that *AR* alleles are associated with differential stage, grade, or survival, the inconsistencies among studies could be attributable to low power in some samples studied to detect effects when stratified by tumor characteristics. In addition, the two samples in which no strong relationship was found were from the United Kingdom (46) and Sweden (47), whereas the populations in which associations were observed included two from the United States (43, 44) and one from China (45). One United States population included a substantial proportion of cases diagnosed before the advent of PSA screening (42), as was the case in the Chinese sample (45). Therefore, population differences in the use of prostate cancer screening may also affect the associations, even after relevant tumor characteristics are considered.

CYP3A4. *CYP3A4* is involved in the oxidation of testosterone to 2β-, 6β-, or 15β-hydroxytestosterone (58), which is less biologically active that testosterone. Variants that affect *CYP3A4* activity could therefore alter prostate tumor aggressiveness. A variant in the 5′ untranslated region of *CYP3A4* has been associated with tumor severity in two studies. Rebbeck *et al.* (59) found that Caucasian carriers of a variant *CYP3A4* allele had a higher TNM stage and Gleason grade than men who did not carry this variant. The effect on tumor stage was most pronounced in men diagnosed at a relatively old age who reported no family history of prostate cancer. Subsequently, Paris *et al.* (60) reported the same association with tumor grade and stage, also with stronger effects in older men. Although this association has been reported in only two studies, the results are consistent with an effect of *CYP3A4* on the natural history, and possibly prognosis, of prostate cancers. The observation that *CYP3A4* genotype is associated with higher clinical stage and grade prostate tumors is consistent with the hypothesis that *CYP3A4* may be associated with androgen-mediated increases in prostate cell proliferation or growth.

CYP17. *CYP17* is involved in the biosynthesis of testosterone. A single nucleotide polymorphism in the promoter region of *CYP17* has been widely studied in prostate cancer and has been generally inferred in most studies to be associated with prostate cancer risk (38). It has been hypothesized that this variant is associated with increased *CYP17* activity, which makes it a candidate for consideration as a factor associated with prostate tumor growth, progression, and therefore natural history. However, this variant was not found to be associated with circulating steroid hormone levels in men (61, 62). In addition, studies to date have generally reported that *CYP17* genotypes are not associated with clinical characteristics of tumors including tumor stage or grade (51, 54). However, Kittles *et al.* (63)

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Table 1 Examples of reports relating inherited genotypes with characteristics of prostate cancers at diagnosis

Gene (OMIN no.), chromosome	Trait[a]	Positive association: Reference, No. of cases studied	No association: Reference, No. of cases studied
AR(313700), Xq11–q12			
(CAG_n)	Grade	Giovannucci *et al.* (41) 1997, $n = 587$	Edwards *et al.* (46) 1999, $n = 178$; Bratt *et al.* (47) 1999, $n = 190$; Stanford *et al.* (43) 1997, $n = 301$; Correa-Cerro *et al.* (76) 1999, $n = 132$; Hsing *et al.* (45) 2000, $n = 190$
	Surv	Giovannucci *et al.* (41) 1997, $n = 587$; Nam *et al.* (49) 2001, $n = 318$	Edwards *et al.* (46) 1999, $n = 178$
	TNM	Giovannucci *et al.* (41) 1997, $n = 587$; Ingles *et al.* (42) 1997, $n = 57$; Hakimi 1997, $n = 59$	Edwards *et al.* (46) 1999, $n = 178$; Bratt *et al.* (47) 1999, $n = 190$; Stanford *et al.* (43) 1997, $n = 301$; Hsing *et al.* (45) 2000, $n = 190$
(GGN_n)	Grade	Stanford *et al.* (43) 1997, $n = 301$; Hsing *et al.* (45) 2000, $n = 190$; Correa-Cerro *et al.* (76) 1999, $n = 132$	Platz *et al.* (42) 1998, $n = 582$; Edwards *et al.* 1999, $n = 178$
	Surv	Edwards *et al.* (46) 1999, $n = 178$	Platz *et al.* (42) 1998, $n = 582$
	TNM	Stanford *et al.* (43) 1997, $n = 301$; Hsing *et al.* (45) 2000, $n = 190$	Platz *et al.* (42) 1998, $n = 582$; Edwards *et al.* (46) 1999, $n = 178$
CYP3A4 (124010), 7q22.1 (5′ UTR A-290G)	Grade	Rebbeck *et al.* (59) 1998, $n = 230$; Paris *et al.* (60) 1999, $n = 174$	
	PSA		Rebbeck *et al.* (59) 1998, $n = 230$
	TNM	Rebbeck *et al.* (59) 1998, $n = 230$; Paris *et al.* (60) 1999, $n = 174$	
CYP17 (202110), 10q24.3 (5′ UTR *Msp*I)	Grade		Lunn *et al.* (51) 1999, $n = 108$; Habuchi *et al.* (54) 2000, $n = 252$;Haiman *et al.* (62) 2001, $n = 590$; Yamada 2001, $n = 105$
	TNM		Gsur *et al.* (53) 2000, $n = 44$; Habuchi *et al.* (54) 2000, $n = 252$; Haiman *et al.* (62) 2001, $n = 590$; Yamada 2001, $n = 105$
HPC2 (605367), 17p112 (S217L or A541T)	Grade		Rebbeck *et al.* (39) 2000, $n = 359$; Xu *et al.* (70) 2001, $n = 249$; Vesprini *et al.* (40) 2001, $n = 431$
	PSA	Rebbeck *et al.* (39) 2000, $n = 359$	Vesprini *et al.* (40) 2001, $n = 431$
	TNM		Rebbeck *et al.* (39) 2000, $n = 359$; Xu *et al.* (70) 2001, $n = 249$; Vesprini *et al.* (39) 2001, $n = 431$
PSA (176820), 19q13	TNM	Xue *et al.* (70) 2000, $n = 57$	
PTEN (601728), 10q23.3 (IVS4 5-bp insertion)	Grade		Nathanson *et al.* (72) 2001, $n = 248$; George *et al.* (73) 2001, $n = 600$
	PSA	Nathanson *et al.* (72) 2001, $n = 248$	
	TNM		Nathanson *et al.* (72) 2001, $n = 248$; George *et al.* (73) 2001, $n = 600$
SRD5A2 (264600), 2p23 (A49T)	Grade	Makridakis *et al.* (48) 1999, $n = 216$	Jaffe *et al.* 1999, $n = 265$; Mononen, *et al.* (68) 2001, $n = 449$
	PSA		Jaffe *et al.* 1999, $n = 265$
	TNM	Jaffe *et al.* 2000 (67), $n = 265$; Makridakis *et al.* (48) 1999, $n = 216$	Mononen *et al.* (68) 2001, $n = 449$
(V89L)	Grade		Febbo *et al.* (50) 1999, $n = 584$; Jaffe *et al.* 1999, $n = 265$
	PSA		Jaffe *et al.* 1999, $n = 265$
	Surv	Nam *et al.* (69) 2001, $n = 318$	
	TNM		Febbo *et al.* (50) 1999, $n = 584$; Jaffe *et al.* 1999, $n = 265$
VDR (601769), 12q12-q14[b]			
(exon 2, *Fok*I)	Grade		Correa-Cerro *et al.* (76) 1999, $n = 132$
	TNM		Chokkalingam *et al.* 2001, $n = 191$
(intron 8, *Bsm*I)	Grade	Ingles *et al.* 1998, $n = 151$	Ma *et al.* (55) 1998, $n = 372$
	TNM	Ingles *et al.* 1998, $n = 151$	Ma *et al.* (55) 1998, $n = 372$; Chokkalingam *et al.* 2001, $n = 191$
(exon 9, *Taq*I)	Grade		Taylor *et al.* (57) 1996, $n = 108$; Ma *et al.* (55) 1998, $n = 372$
	TNM		Taylor *et al.* (57) 1996, $n = 108$; Ma *et al.* (55) 1998, $n = 372$; Blazer *et al.* (56) 2000, $n = 77$
(3′ UTR Poly A)	Grade	Ingles *et al.* 1998, $n = 151$; Correa-Cerro *et al.* (76) 1999, $n = 132$	
	TNM	Ingles *et al.* (42) 1997, $n = 57$; Ingles *et al.* 1998, $n = 151$	Blazer *et al.* (56) 2000, $n = 77$

[a] Characteristics include: Grade, tumor grade (usually Gleason score); PSA, PSA levels; Surv, biochemical relapse-free survival, disease-free survival, or overall survival; TNM, tumor stage (including metastatic, extracapsular, or node positive disease *versus* localized disease); Tx, treatment response.
[b] Because of the strong linkage disequilibrium among alleles in *VDR*, not all combinations of alleles and genotypes are reported here.

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reported that this *CYP17* variant was associated with higher stage and grade tumors. Although some of the reports involved relatively small sample sizes, the consistency of the reports showing no association with tumor characteristics suggests that upstream pathways of testosterone synthesis may be less likely to be involved in the prediction of prostate tumor characteristics than downstream pathways. These downstream pathways include those involving *CYP3A4*, *SRD5A2*, or *AR*, for which some positive associations with tumor characteristics have been reported.

SRD5A2. *SRD5A2* is involved in the conversion of testosterone to dihydrotestosterone, which has greater androgen activity in the prostate than testosterone itself (64). When bound to the androgen receptor, dihydrotestosterone activates a number of genes involved in prostate development and growth (65). A number of missense variants in *SRD5A2* have been reported. Two of these (*A49T* and *V89L*) have relatively high population frequencies and may be associated with altered testosterone metabolism or prostate cancer risk (48, 66). These and other studies have also evaluated the relationship of these two variants with characteristics of prostate tumors. Makridakis *et al.* (48) and Jaffe *et al.* (67) reported that the A49T variant was associated with altered tumor stage or grade. However, Jaffe *et al.* (67) showed no association with pretreatment PSA level. In contrast, Mononen *et al.* (68) showed no association with A49T and tumor characteristics in a Finnish population. Two studies to date have shown no association of the V89L variant and tumor stage, grade, or PSA level (48, 67). Nam *et al.* (69) reported that the V89L variant was associated with biochemical failure (*i.e.*, recurrence) in men who underwent radical prostatectomy. Although the results are not completely consistent across all studies, the data suggest that genotypes at *SRD5A2* may be associated with natural history of prostate cancer and possibly clinical outcome.

Genes in Other Pathways

HPC2/ELAC2. *HPC2/ELAC2* has been identified as a susceptibility gene for prostate cancer and has been suggested to predict characteristics of prostate tumors at diagnosis. Rebbeck *et al.* (39) examined the effects of germ-line Ser217Leu and Ala541Thr polymorphisms at *HPC2/ELAC2* on characteristics of prostate tumors using 265 men of all races with incident prostate cancer who were treated by radical prostatectomy. Homozygous Leu217 genotypes were found in significantly higher frequency among men diagnosed with a PSA >10 ng/ml compared with men diagnosed with PSA ≤ 10 ng/ml (odds ratio, 4.15; 95% confidence interval, 1.34–12.80). However, no other tumor characteristics were found to differ by genotype in this study or two subsequent studies (27, 40). Xu *et al.* (27) reported no difference in tumor stage or grade by *HPC2* genotype but did not report differences in PSA levels using a clinic-based sample. Vesprini *et al.* (40) studied a group of screened detected cancers and found no difference in any tumor characteristic. However, the population of screened detected cases is different from those in the other two samples; therefore, the differences seen in the study of Vesprini *et al.* (40) could in part be explained by differences in sample ascertainment. Thus, it remains unclear whether genotypes at *HPC2/ELAC2* influence pretreatment PSA levels.

KLK3/PSA. The *KLK3* gene encodes PSA and contains an androgen response element that regulates PSA expression by binding of *AR*. Xue *et al.* (70) reported that a *KLK3* gene promoter variant was associated with advanced disease (defined as having extracapsular extension or nodal/distant metastases) but not localized disease. However, the number of cases studied here (26 advanced and 31 localized) was small, and additional studies will be required to confirm this result.

PTEN. Loss of heterozygosity at chromosome 10q23–25 and allelic loss of the *PTEN* gene is frequently observed in prostate tumors. This suggests that this locus is a target of inactivation. The absence of *PTEN* expression in prostate tumors is highly correlated with Gleason score and advanced stage and appears to play a role in prostate cancer progression (71). Therefore, germ-line mutations in *PTEN* have been considered as modifiers of prostate cancer risk or tumor characteristics. Unfortunately, no common polymorphisms in the coding region of *PTEN* have been reported, although several intronic variants have been identified, including a 5-bp insertion (TCTTA) at IVS4 + 109. Two studies to date have evaluated this variant in relation to prostate tumor characteristics (72, 73), and neither reported an association with tumor characteristics, despite having adequate statistical power to detect it, had it existed. Therefore, there is little reason to believe that germ-line mutations in *PTEN* will be associated with prostate cancer natural history or prognosis.

VDR. Vitamin D can inhibit prostate tumor growth through the *VDR* (74, 75). Therefore, *VDR* has been a candidate for associations with prostate tumor characteristics. A variety of variants has been reported in *VDR*, including a *Fok*I RFLP in exon 2, a *Bsm*I RFLP in intron 8, a *Taq*I RFLP in exon 9, and a poly(A) microsatellite repeat variant in the 3′ untranslated region. The functional significance of these variants is not clear, and there may be linkage disequilibrium between the alleles of these variants. Each of these variants has been studied in the context of prostate tumor characteristics. Ingles *et al.* (42) have reported that the *Bsm*I and poly(A) variants are associated with tumor stage or grade, and Correa-Cerro *et al.* (76) has reported an association of the poly(A) variant with tumor grade. However, a number of other studies (Table 1) have not reported similar effects. Given the limited information about the functional and multiallelic relationships of *VDR* variants, additional research may be required before it will be clear what role each of these variants may have on prostate tumor characteristics.

Genes Involved in Response to Treatment and Chemoprevention

Response to prostate cancer treatment is determined in part by drug pharmacokinetics that control levels of the absorption and dissemination and drug in the bloodstream as well in target tissues. In addition to pharmacodynamic determinants, the metabolic activation and excretion of drugs may also determine the amount and type of drug at the target tissue. Inherited genetic variation may influence the structure or amount of these agents to influence drug pharmacodynamics and metabolism and, therefore, may predict interindividual variability in drug response or toxicity. A paradigm for the role of inherited genotype dictating treatment regimen is the use of thiopurine-containing drugs that are metabolized by *TPMT* (77). *TMPT*-deficient individuals comprise a small subset of most populations studied to date, but these individuals can experience clinically significant toxicities if exposed to standard doses of thiopure drugs. Therefore, knowledge of an individual's *TPMT* genotype is crucial to treatments that involve these agents. Other classes of enzymes, including dihydropyrimidine dehydrogenase, aldehyde dehydrogenases, glutathione *S*-transferases, UDP glucuronosyl-transferases, and cytochromes P-450 may also have pharmacogenetic significance in determining cancer chemotherapy (78).

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Aside from surgical treatments, therapies for prostate cancer tend to involve hormone therapies or exposure to radiation. In both cases, inherited genotypes may influence the metabolism or response to exposures. In addition, a number of prostate cancer chemopreventive agents have been proposed or are being studied. The efficacy of these agents in preventing prostate cancer could also be determined by inherited genotypes. For example, *CYP3A4* is known not only to metabolize testosterone but also finasteride (Proscar; Ref. 79), which is being evaluated as a prostate cancer chemopreventive agent. Therefore, inherited genotypes at *CYP3A4* could influence response or toxicity to this chemopreventive regimen.

Unfortunately, little data exist that address the role of inherited genotypes in determining optimal prostate cancer treatment or chemoprevention strategies. Bratt *et al.* (47) reported that response to endocrine therapy (orchiectomy, gonadotropin-releasing hormone, or bicalumide monotherapy) improved by 25% for each increase in CAG triplet repeat length in *AR* or a 4-fold better prognosis comparing men with 25 *versus* 19 *AR*-CAG repeats. Despite a relatively small sample size ($n = 73$), this relationship remained marginally significant even after adjusting for pretreatment level of PSA and tumor grade and stage. These results exemplify the type of relationship the inherited genotype may have on prognosis in response to therapy. However, Bratt *et al.* (47) also reported that longer *AR*-CAG repeat length was also associated with tumor stage. Thus, a difficulty in assessing these types of data is to tease apart the value of the inherited genotype to predict natural history of disease *versus* response to treatment, or whether both phenomena contribute simultaneously to outcome. Studies that want to address this problem need to be designed to be able to specifically tease apart natural history from treatment response.

Implications for Studies of Prostate Cancer Treatment and Prevention

A large proportion of prostate cancer may be indolent in nature and treatments for nonfatal prostate cancer may themselves not be benign. Therefore, an important area of prostate cancer research is to identify predictors of clinical outcome. A number of histopathological factors and somatic biomarkers have been proposed as predictors of disease natural history or prognosis. The data reviewed here suggest that inherited genotype may provide similar predictive information. This information could be used to: (*a*) identify individuals at risk of prostate cancer with poor outcomes for heightened screening or prevention modalities; and (*b*) identify the optimal treatment including type, timing, or dose.

The ability to obtain this information requires that epidemiological and clinical studies be designed specifically to address these issues. For the most part, the studies reporting genotype-tumor trait effects in the past have not been designed specifically to study these relationships but instead were reported in the context of etiological studies using a case-control or cohort design. Often, the case inclusion-exclusion criteria are not adequately defined or sometimes inappropriately collected for the evaluation of natural history and prognosis. Studies are often not specifically designed to have adequate statistical power for the evaluation of these questions. In particular, prospective follow-up of a well-defined cohort of patients may be inadequate or incomplete. Evidence for the sample size limitation of many studies is given by the many reports in which genotype was inferred to have no effect when the associated *P*s fell in the 0.05–0.10 range with some moderately large effect sizes.

As in other areas in which molecular epidemiological association studies are conducted, inconsistent inferences between studies are common. In part, limited statistical power may play a role in these inconsistent inferences. In addition, differences in the definition and distribution of tumor characteristics including stage and grade among studies may affect the consistency of inferences. For example, screening practices at the time of case ascertainment may result in inconsistencies in the nature of the case sample studied. This information is often not available or not presented, and thus inconsistencies among studies that could be explained by very different effects in different study populations may be interpreted as inconsistency of results. Future studies in this area should report and evaluate the distribution of screening and tumor stage or grade in studies that evaluate inherited genotype and tumor characteristics, natural history, or prognosis. Similarly, differences among study populations with respect to ethnicity or geography could affect the inferences of a study. These differences may reflect real differences across populations and not a failure of the methodology to detect these effects. This should also be accounted for in the interpretation of study results. A final consideration should be the simultaneous consideration of multiple factors simultaneously, to determine whether inherited genotype provides additional information about natural history, prognosis, or treatment response that is independent of that found in traits that are more easily obtained, including histopathological characteristics. Inherited genotype information will only have value in predicting outcome if it provides readily accessible predictive or prognostic information beyond that routinely used and collected on these patients.

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