Human Molecular Genetics, 2004, Vol. 13, Review Issue 1 **R103–R121**
DOI: 10.1093/hmg/ddh072
Advance Access published on January 28, 2004

The complex genetic epidemiology of prostate cancer

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Received December 31, 2003; Revised and Accepted January 5, 2004

Prostate cancer is the most frequent cancer among men in most developed countries, yet little is known about its causes. Older age, African ancestry and a positive family history of prostate cancer have long been recognized as important risk factors. The evidence that genetics probably plays a critical role is based on a variety of study designs, including case–control, cohort, twin and family-based, all of which are reviewed in detail. The search for prostate cancer susceptibility genes by linkage studies offered early hope that finding genes would be as 'easy' as finding genes for breast cancer and colon cancer susceptibilities. However, this hope has been dampened by the difficulty of replicating promising regions of linkage. This review provides updates on recent developments, and a broad view of the disparate findings from different linkage studies. Early linkage results have provided targeted candidate regions for prostate cancer susceptibility loci, including *HPC1* on chromosome 1q23–25, *PCAP* on chromosome 1q42–43, *CAPB* on chromosome 1p36, linkage to chromosome 8p22–23, *HPC2* on chromosome 17p, *HPC20* on chromosome 20q13, and *HPCX* on chromosome Xq27–28. These linkage findings lead to refined mapping and mutation screening of several strong candidate genes, including *ELAC2*, *RNASEL* and *MSR1.* Up to now, a total of 10 genome-wide linkage scans for prostate cancer susceptibility have been completed, and are reviewed. Furthermore, recent findings that Gleason's grade, a measure of aggressiveness of prostate cancer, is linked to several genomic regions are reviewed. Finally, the roles of environmental and dietary risk factors, and common genetic polymorphisms of genes likely to play a role in common forms of prostate cancer, are briefly discussed within in the context of searching for genes that influence prostate cancer risk.

INTRODUCTION

Prostate cancer is the most frequent cancer among men in most developed countries, yet little is known about its causes. Older age, African ancestry and a positive family history of prostate cancer have long been recognized as important risk factors, yet we are only at the early stage of unraveling the complex genetic and environmental influences on this disease. Over the past 20 years, the body of evidence that genetics plays a key role has grown immensely, ranging from familial aggregation and twin studies, to family-based linkage studies, to detection of likely functional genes via mutation screening, to molecular epidemiological studies of both rare and common polymorphisms of candidate genes. However, the evidence also points toward a much more complex genetic basis of prostate cancer than initially anticipated. This review highlights key findings from a wide range of study designs in an effort to guide the reader through the current understanding of the genetic factors that influence the susceptibility to prostate cancer, and possibly those that modulate its clinical course of disease. Much of this review is focused on genes that are likely to be involved in hereditary prostate cancer, although environmental risk factors and the potential influence of common polymorphic genes are briefly discussed, recognizing that the risk for prostate cancer may result from a complex interaction of all of these factors.

INCIDENCE OF PROSTATE CANCER AND THE INFLUENCE OF PSA

Prostate cancer is a major health burden throughout the world, although there is a large variation in its incidence. The highest rates are in the USA, Canada, Sweden, Australia and France (48.1–137.0 cases per 100 000 person-years during 1988–1992); European countries have intermediate rates (23.9–31.0

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cases per 100 000 person-years), and Asian countries the lowest rates (2.3–9.8 cases per 100 000 person-years) (1). Although the causes of this variation are likely to be differences in screening methods, diet and health-related behaviors, clinical practice patterns and environmental risk factors, the role of genetic differences is unknown. The observation that prostate cancer risk increases for Japanese migrants to Hawaii (2) and Japanese migrants to Los Angeles (3), and the large variation of the incidence of prostate cancer among Chinese in different geographic locations (e.g. Asia versus the USA) (4), suggests that diet and environmental differences play a major role. There is, however, consistent evidence across different racial and ethnic groups that a family history of prostate cancer increases the risk that a man will get prostate cancer. As will be shown, genetics is likely to play an important role in some forms of prostate cancer, which in turn may influence the future prevention, diagnosis and treatment of this disease.

For the USA, the American Cancer Society predicts that during 2003 there will be 220 900 newly diagnosed cases of prostate cancer, that the lifetime probability of developing invasive prostate cancer is 16.67% (about 1 in 6), and that there will be 28 900 deaths due to prostate cancer. For men, prostate cancer is the most frequent of all cancers (33%; followed by lung and bronchus cancers at 14%), and the second most frequent for deaths due to cancer (10% prostate cancer; 31% lung and bronchus cancers) (5). The interpretation of the published literature regarding the potential roles of familial and genetic risk factors on prostate cancer is clouded, however, by changes in how prostate cancer has been diagnosed over the past 15–20 years. In 1986, the Food and Drug Administration approved the prostate-specific antigen (PSA) test for use in monitoring prostate cancer progression. Its use as a screening test for prostate cancer diagnosis increased from 1988 (6). This has had a dramatic influence on local (7) and national trends of prostate cancer incidence (5), with rates increasing greatly during 1988–1992, declining sharply during 1992–1995, and leveling off during 1995–1999 (8,9). Prior to the advent of PSA testing, diagnosis of prostate cancer was primarily by clinical symptoms, or detected by transurethral resection of the prostate for benign prostatic hyperplasia, and the lifetime probability of a clinical prostate cancer diagnosis was only $\sim$ 9% for both Caucasians and African Americans (10). The consequence of PSA screening has been diagnosis of earlier stage disease, with an average lead-time (time by which the PSA advances the diagnosis of prostate cancer) of 3–7 years (11–13). Also, the types of cancers detected during 1988–1992 (when prostate cancer rates were sharply rising, shortly after the advent of PSA screening), are likely to be 'length-biased', whereby cases with a longer natural history of disease progression, and hence less aggressive cancers, tend to be detected by the introduction of the new screening procedure. Hence, the age of diagnosis and the clinical severity of prostate cancer have changed due to the use of PSA, both as a screening tool and as confirmatory evidence for suspicious clinical symptoms. As discussed below, it is very likely that the aggressiveness of prostate cancer is influenced by genes, and so the recent trend for diagnosis of early-stage and less aggressive prostate cancer clouds the interpretation of the historical literature of the genetic epidemiology of this disease.

EPIDEMIOLOGICAL EVIDENCE OF PROSTATE CANCER GENETICS

A positive family history is one of the strongest risk factors for prostate cancer. Approximately 10–15% of men with prostate cancer have at least one relative who is also affected (14,15). Furthermore, there is substantial evidence that genetics is likely to play a key role, at least for men with a positive family history. The evidence for this comes from a variety of study designs, including case–control, cohort, twin, and family-based, all of which are discussed below in greater detail.

Case–control and cohort studies

The case–control design is a powerful and efficient method to evaluate the association of potential risk factors with prostate cancer. A large number of case–control studies have evaluated the risk of a positive family history, and results have consistently shown that having at least one first degree relative affected with prostate cancer conveys an odds ratio (OR) of $\sim$2.5. A word of caution on the interpretation of the OR is warranted for a common disease like prostate cancer. The OR is calculated by categorizing the cases and controls according to presence or absence of prostate cancer among their first-degree relatives, and the OR is used as a measure of association between the presence/absence of disease in the cases/controls and presence/absence of disease in their relatives. For rare diseases, the OR provides a good approximation to the relative risk. In our context, the relative risk is the ratio of the probability of disease for a man with a positive family history divided by the probability of disease for a man with a negative family history. For common diseases, such as prostate cancer, the OR overestimates the true relative risk.

A meta-analysis of 11 case–control studies (14–25) and two cohort studies (26,27) that reported the risk of prostate cancer according to family history among first degree relatives estimated a pooled OR of 2.5 (95% CI 2.2–2.8, with a range of 2.0–3.9) (28). In all but one of these studies, the OR was greater if a brother was affected than if a father was affected. The pooled estimates of ORs were 3.4 if a brother was affected (95% CI 2.9–4.1) and 2.5 if a father was affected (95% CI 2.1–3.1). The OR associated with a positive family history was greater if a man was diagnosed at age $<$65 year (OR of 4.3) than at age $>$65 years (OR of 2.4). Four studies reported the risk of prostate cancer according to having more than one affected first-degree relative, and these ORs ranged from 2.8 to 9.4; the pooled estimate was 3.5. More refined estimates of ORs according to the number of affected first-degree relatives were provided by Steinberg *et al.* (18). They estimated the OR to increase from 2.2 to 4.9 to 10.9 if there were one, two, or three or more affected first-degree relatives. Whittemore *et al.* (15) found somewhat similar results, considering the sparseness of the number of men with more than one affected relative: two or more affected first-degree relatives gave ORs of 9.7 among African Americans, 3.9 among Caucasians, yet only 1.6 among Asian Americans.

Although the findings from these case–control studies suggest shared familial risk factors for prostate cancer, possibly genetic, they can be biased for several reasons. The information about family history is usually obtained after the case is

diagnosed with prostate cancer. This can cause 'referral bias', whereby the cases are more aware of the diagnosis of prostate cancer among family members than the controls, or the cases are more likely to misinterpret prostate problems as cancer. For many case–control studies, it was rare to obtain pathologic confirmation of cancers among relatives. An alternative to the case–control study design is a cohort study in which men are followed until their current age, occurrence of prostate cancer or death. A significant advantage of registries and cohort studies is that they are not as prone to recall bias. In addition, these types of cohort studies allow estimation of relative risks, in place of approximating relative risks by ORs. Two studies used the relatives of cases and the relatives of controls as cohorts, and computed the relative risk of disease among the relatives according to the disease status of cases/controls. Using 690 consecutive cases undergoing radical prostatectomy and diagnosed prior to 1989, Isaacs *et al.* (21) estimated a relative risk of 1.76 for first-degree relatives. Using 101 incident cases diagnosed during 1988–1995 from a population-based registry in Iowa, Cerhan *et al.* (29) estimated a relative risk of 3.2 for first-degree relatives; this risk was greater if a brother had prostate cancer (RR = 4.5) than if a father had prostate cancer (RR = 2.3). Without availability of controls, two other studies compared the observed number of prostate cancers among relatives of cases with the number expected, where the expected numbers were calculated according to population-based age-specific incidence rates. The ratio of the observed to expected number of cancers is called a standardized incidence ratio (SIR), which approximates a relative risk. Grönberg *et al.* (30) found that sons of Swedish men affected with prostate cancer had an SIR = 1.70, and Cunningham *et al.* (31) found that first-degree relatives of cases who were diagnosed with prostate cancer at a Houston VA medical center had an SIR = 1.61. These cohort studies provide results that are consistent with the ORs provided by case–control studies, although with somewhat lower estimates of relative risk.

A consistent finding across many studies has been an increased risk of prostate cancer when a brother is affected with prostate cancer compared with when a father is affected. Some have suggested that this could be caused either by X-linked or recessive genetic components (32,33). However, diagnosing a man with prostate cancer may increase the chance that his male relatives will seek a prostate cancer screening test. This can bias the relative risk for affected brothers to be greater than that for affected fathers. The study by Steinberg *et al.* (18), which also found the OR to be greater when a brother was affected than when a father was affected, was conducted before PSA screening was introduced, strengthening the hypothesis that there may be a genetic cause for this difference in relative risks. To address this issue more directly, Staples *et al.* (34) conducted a study in Australia for men diagnosed with prostate cancer during 1994–1998, and estimated the OR to be 3.9 when a brother was affected, and 2.9 when a father was affected. When the data was stratified according to year of diagnosis of the relative (prior to, or after, 1992), the ORs for when a brother was affected were 3.1 (prior to 1992) and 3.9 (after 1991), and for when a father was affected, 2.8 (prior to 1992) and 2.5 (after 1991). The authors interpreted this to mean that the introduction of PSA testing may have inflated the risks associated with an affected brother. Further evidence that PSA screening may influence the estimates of familial relative risks come from PSA screening studies. A randomized prostate trial of the efficacy of PSA screening in Finland estimated that the relative risk of screen-detected prostate cancer, comparing men with a positive versus negative family history, was 1.3 (35). In a screening study in Quebec (33), the estimated relative risk was 1.7 for an affected first-degree relative (relative risk of 2.6 if a brother was affected). Because these relative risks are somewhat less than those reported for case–control and cohort studies based on clinical (as well as PSA-detected) diagnoses, it may be that prostate cancers detected solely by PSA screening are less likely to have a genetic etiology.

Most of the above studies of familial aggregation of prostate cancer were based on Caucasians from the USA, Canada, Sweden and Australia. There have been a number of reports, however, that demonstrate similar familial risks for different racial/ethnic groups. Monroe *et al.* (32) conducted a population-based cohort study of African Americans, Hispanics, Japanese and Whites, and found similar risks for all four groups (relative risks ranged 1.8–2.5 if fathers were affected). Whittemore *et al.* (15) found that the ORs due to a positive family history among first-degree relatives were 1.9 for Caucasians, 2.7 for Asian Americans, and 3.0 for African Americans, and these differences were not statistically significant. Cunningham *et al.* (31) found similar SIRs for African Americans (SIR = 1.58) and non-African Americans (SIR = 1.65). Among black men from Jamaica, Glover *et al.* (24) estimated an OR of 2.1 when a first-degree relative was affected with prostate cancer. Finally, Stone *et al.* (36) found similar ORs according to positive family history for Hispanics (OR = 2.7) and non-Hispanic Whites (OR = 2.0). In summary, although the incidence and outcome for prostate cancer may differ among different racial and ethnic groups, the increased risk for prostate cancer attributed to family history of this disease is quite consistent across different ethnic backgrounds, supporting the possibility of a common genetic basis for this disease.

Family-based segregation analyses

Family-based segregation analyses provide a quantitative method to evaluate whether the observed aggregation of disease in a series of families fits the expected distribution based on a genetic (or purely environmental) model. The genetic models are based on Mendelian segregation of alleles within families, the population frequency of the putative susceptibility allele, and the penetrance of the underlying genotypes (usually age-dependent penetrance). To date, eight segregation analyses of prostate cancer have been published, using different types of pedigrees, different sources for ascertainment, and from different countries. These studies are summarized in Table 1. The studies by Carter *et al.* (37), Schaid *et al.* (38) and Verhage *et al.* (39) are similar because all three selected probands who were eligible for a radical prostatectomy, and hence have localized disease with a good prognosis. All three studies found that the best fitting model was a rare autosomal dominant susceptibility allele (allele frequency ranging 0.003–0.006) with a high life-time penetrance for carriers (ranging 88–97%). The study by Valeri *et al.* (40) was based on an unselected series of hospital-based probands, and

Table 1. Studies of complex segregation analysis of prostate cancer

Author	No. families	Family type[a]	Population	Proband[b]	Most likely genetic model[c]	Lifetime penetrance (%)	Disease allele frequency
Carter, 1992 (37)	691	Nuclear (F,B)	USA	RP	AD	88	0.003
Grönberg, 1997 (41)	2857	Nuclear (F,S)	Sweden	Population registry	AD	63	0.017
Schaid, 1998 (38)	4228	First-degree (F,B,S)	USA	RP	AD	89	0.006
Verhage, 2001 (39)	1119	Nuclear (F,B)	USA	RP	AD	97	0.004
Cui, 2001 (42)	1476	Pedigree (F,B,U)	Australia	Population registry	AD AR or X	70 (AD) 100 (AR or X)	0.017 (AD) 0.084 (AR)
Gong, 2002 (43)	1719	First-degree (F,B,S)	USA, Canada	Population registry	AD (or MF)	75 (African American, White) 44 (Asian American)	0.024
Conlon, 2003 (44)	263	Pedigree	USA	Multiplex for linkage	2-3 loci (2 AD)	n.a.	n.a.
Valeri, 2003 (40)	691	Nuclear (F,B)	France	Hospital	AD	86% (F) 99% (B)	0.0003

[a]Family type composed of: father (F), brothers (B), sons (S), uncles (U).
[b]Proband ascertained according to: radical prostatectomy (RP), population registry, hospital series of cases, or multiplex pedigrees selected for linkage analyses.
[c]Genetic models: autosomal dominant (AD), autosomal recessive (AR), X-linked (X), multifactorial (MF).

they too found that an autosomal dominant model fit best, with a 10-fold smaller allele frequency (0.0003) and lifetime penetrance of 99% for men in the same generation as the proband, and of 86% for men in the same generation as the probands' fathers. A unique aspect of the analysis by Valeri *et al.* was allowance for residual correlations among family members that were not explained by the genetic model. They found that there was unexplained dependence among brothers. The results from Schaid *et al.* (38) were also consistent with unexplained departures from a simple autosomal dominant model. They found that the autosomal dominant model provided a good fit only when probands were diagnosed at age <60 years and departure of parental genotype frequencies from Hardy–Weinberg equilibrium was allowed. This departure was required because there was an excess of putative homozygous carriers compared with that predicted by Hardy–Weinberg frequencies. Furthermore, the age-adjusted relative risk for brothers was greater than that for fathers. Hence, the studies of Schaid *et al.* and Valeri *et al.* suggest that there may be additional genetic or shared environmental factors that the simple autosomal dominant model cannot explain.

In contrast to the above hospital-based selection of probands, the study by Grönberg *et al.* (41) selected probands from a population-based registry in Sweden, which did not use PSA to screen for prostate cancer. This study also found that an autosomal dominant model fit best, but with a more frequent susceptibility allele (0.017) and a lower penetrance (63%). A limitation of this study, and those discussed above, is that the analyzed pedigrees were only first-degree relatives of the probands (chosen because the family history provided by the probands is most accurate for first-degree relatives, but less so for more distant relatives). These types of small pedigrees, for which prostate cancer information comes mainly from fathers and brothers, because sons are often too young to be at risk for prostate cancer, provide limited information to discriminate between autosomal or X-linked and dominant or recessive modes of inheritance, particularly when penetrance is incomplete and there is a high rate of phenocopies. The study by Cui *et al.* (42) overcomes some of this limitation, by using paternal and maternal uncles, in addition to fathers and brothers of the probands. Their probands were sampled from a population-based registry in Australia. Furthermore, they evaluated genetic models that allowed for either one or two loci. The model that provided the best fit to their data included a rare autosomal dominant allele that has large risk at younger ages, and a more common allele that is either autosomal recessive or X-linked, and has a larger effect at older ages. The recessive component gave a slightly better fit than the X-linked component, but it was difficult to accurately discriminate between these two genetic effects. Because the risk alleles from the putative dominant and recessive loci were rare (frequency of 0.017 for dominant allele and frequency of 0.084 for recessive allele), it would be very rare for a single pedigree to segregate susceptibility alleles from both loci. Hence, their two-locus model is essentially a model of heterogeneity, with early-onset pedigrees more likely explained by an autosomal dominant effect, and late-onset pedigrees more likely explained by either an autosomal recessive or X-linked effect. It is interesting that the autosomal dominant allele frequency and penetrance from this Australian population-based sample are similar those observed by Grönberg *et al.* for their Swedish population-based sample. A third population-based sample of White, African American, and Asian American probands from the USA and Canada were evaluated for their family history, and segregation analysis found that an autosomal dominant model gave an adequate fit, with an estimated allele frequency of 0.024, and life-time penetrances of 75.3% for African Americans and Whites, and 44.4% for Asian-Americans (43). Both recessive and X-linked models fit poorly. However, a mutifactorial model, which allows for multiple genes, each having low penetrance, fit just as well as the autosomal dominant. Because the multifactorial model requires fewer parameters than the autosomal dominant model, the authors suggested that the multifactorial model may be the best choice.

Finally, the study by Conlon *et al.* (44) used a completely different strategy. They analyzed highly selected pedigrees that were ascertained for a linkage study, and used a statistical method that simultaneously estimates the number of susceptibility loci, the allele frequencies, and their effects on age of diagnosis (dominant /recessive), as well as allowing for covariates.

Importantly, they found that allowing for prostate cancer diagnosis before or after 1988 (a surrogate for whether or not the cancer was diagnosed by PSA screening) improved the fit of their models. The best fitting model included two or three susceptibility loci, which explained 92% of the variation of age at diagnosis, and the two loci with largest effects were autosomal dominant. The novelty of their approach is the flexibility in the genetic model. However, this study requires cautious interpretation, because it was impossible to correct for how the pedigrees were ascertained, so allele frequency estimates are inflated, as might be the genetic effects on age of diagnosis. Furthermore, because their ascertainment of pedigrees favored those that appeared to have autosomal dominant transmission, it is not surprising that the best fitting model included dominant effects. The importance of this study is that it shows that many of the pedigrees selected for genetic linkage studies of prostate cancer may not be explained by a single locus.

Twin studies

Although excessive aggregation of prostate cancer within families suggests that genes may play a role, family studies cannot distinguish between genetic and non-genetic causes. In contrast, twin studies can provide information on genetic etiology. If the concordance rate of prostate cancer is greater for monozygotic (MZ) than dizygotic (DZ) pairs of twins, then genetic effects are likely to be involved, since MZ twins share 100% of their genes and DZ twins share 50% of their genes. A critical assumption is that shared environmental factors are the same for MZ and DZ twins, including health-related behaviors. For example, it is assumed that screening for prostate cancer is the same for MZ and DZ twin pairs, which is much more likely than similar screening practices for men of different generations in family studies. A number of twin studies of prostate cancer have been published, but some of them (45,46) are incorporated into a recent large study of twins by Lichtenstein *et al.* (47) based on Swedish, Danish and Finnish twin registries. This study estimated that the probandwise concordant rate (interpreted as the recurrence risk in a co-twin of an affected man) was 21.1% for MZ twins and 6.4% for DZ twins, and that 42% of the risk of prostate cancer can be explained by heritable factors. However, the interpretation of this heritability is problematic. For example, if the genetic relative risk for prostate cancer is constant over different populations, but the prevalence of disease changes, then the heritability will also change. Careful discussion of these issues, along with alternative interpretations of the twin study by Lichtenstein *et al.*, is provided by Risch (48). In this report, Risch emphasizes that the familial risk ratio, which is the risk of disease for a given type of relative divided by the population prevalence, is a simple, yet meaningful measure of genetic risk. For MZ twins this risk ratio is denoted λ_M, and for DZ twins, λ_D. Furthermore, the ratio $R_{MD} = (\lambda_M - 1)/(\lambda_D - 1)$ can provide genetic insights. This ratio is $\sim$2 for a disease caused by rare dominant genes, allowing for different rare genes in different families (locus heterogeneity). In contrast, for a recessive gene, this ratio is $\sim$4 if the gene is rare, but approaches 2 for a common allele. However, if the risk for disease is associated with multiple interacting alleles (i.e. multiplicative effects), then R_{MD} can achieve values much greater than 2. When applied to prostate cancer among twins in the Lichtenstein study, Risch estimated that $R_{MD} = 3.86$, and suggested that prostate cancer may not be explained by independent rare autosomal dominant genes, but maybe by recessive and/or multiple interacting genes.

Another large study of World War II veteran twins from the USA reported that the probandwise concordant rate was 27.1% for MZ twins and 7.1% for DZ twins (49). The results from this study are reanalyzed according to the methods of Risch, and presented in Table 2, along with the results from Lichtenstein *et al.* This table illustrates that these two twin studies are remarkably consistent in terms of prevalence of prostate cancer, the probandwise concordance rates, the relative risks to co-twins, and the MZ : DZ ratio. In particular, this R_{MD} ratio is much larger than 2. These two studies represent 1903 affected men from 34 487 twin pairs. The weighted average R_{MD} across both studies, using the total number of pairs from each study as weights, is 4.46. This provides strong evidence that the genetics of prostate cancer is much more complex than rare autosomal dominant mutations.

Definition of hereditary PC

Hereditary prostate cancer has been defined by Carter *et al.* (50) as families that meet at least one of the following three criteria: (1) a cluster of three or more relatives affected with prostate cancer in any nuclear family; (2) the occurrence of prostate cancer in each of three successive generations in either of the proband's paternal or maternal lineages; or (3) a cluster of two relatives, both affected with prostate cancer at 55 years of age or younger. This definition is somewhat biased towards autosomal dominant transmission, and would likely miss some families with autosomal recessive or X-linked transmission. Nonetheless, it has been an operational definition used in a large number of studies, particularly those focused on linkage. In an effort to discriminate between hereditary and non-hereditary forms of prostate cancer, a number of investigators have applied the Carter criteria to prostate cancer cases, in order to explore the clinical features that might discriminate between genetic and non-genetic forms of this disease. No clinical or pathologic characteristics have been found to differ between hereditary and non-hereditary forms of prostate cancer (50,51), and the main difference is an earlier age of diagnosis for hereditary prostate cancer, 6–7 years (51). Hence, based solely on clinical information, it has been difficult to discriminate between likely phenocopies versus genetic cases within pedigrees, as well as to form homogeneous subsets of pedigrees that are likely to be enriched for susceptibility genes.

Familial co-aggregation of prostate and other cancers

A number of studies have suggested that prostate cancer and female breast cancer tend to occur in some families at frequencies greater than expected by chance alone. It has been argued that there may be a common genetic basis for prostate cancer and breast cancer, since they are the most common cancers with approximately equal life-time risks, they are both strongly influence by steroid hormones, gonadal removal

Table 2. Summary of twin studies by Lichtenstein *et al.* (47) and Page *et al.* (49)

Twin study	Twin type	No. of concordant affected pairs (C)	No. of discordant pairs (D)	Total no. pairs[a] (N)	Probandwise concordance rate, %	Prevalence of prostate cancer,[b] % (K)	Relative risk[c] (λ)	MZ : DZ ratio[d] (R_{MD})
Lichtenstein	MZ	40	299	723	21.1	2.34	8.05	3.85
	DZ	20	584	13 769	6.4	2.27	2.83	
	Total	60	883	21 000		2.39		
Page	MZ	57	306	5933	27.1	3.54	7.67	5.42
	DZ	17	446	7554	7.1	3.18	2.23	
	Total	74	752	13 487		3.34		

[a]The total number of MZ and DZ pairs for the study by Page *et al.* were kindly provided by personal communication from Dr William Page.
[b]$K = (2C + D)/(2N)$.
[c]$\lambda = 4CN/(2C + D)^2$.
[d]$R_{MD} = (\lambda_M - 1)/(\lambda_D - 1)$.

reduces the risk of cancer in both sexes, and antiestrogens possibly prevent breast cancer and antiandrogens possibly prevent prostate cancer [see Lopez-Otin and Diamandis (52), for a review]. Although some epidemiologic evidence supports this, not all data regarding the potential familial association between breast and prostate cancers are consistent. A number of studies selected female probands with breast cancer, and found that male relatives were at an increased risk for prostate cancer (26,53–56). Other studies, also with female breast cancer probands, did not find an elevated risk of prostate cancer among relatives (57,58). Differences in these findings may be partly attributed to how female probands were selected, because recent data suggests that the risks for prostate cancer may be greatest when female probands are diagnosed with breast cancer at an extremely early age, less than 36 years (59).

When selecting male prostate cancer probands, some studies have found an elevated risk of breast cancer among female relatives (14,17,60,61), while others have not found such an elevated risk (21,62–64). Sellers *et al.* (65) found that a family history of both prostate and breast cancer increased the risk for postmenopausal breast cancer among relatives, compared with a family history of only breast cancer. Cerhan *et al.* (29) found that for probands with prostate cancer, the prostate cancer risk to their relatives increased if a mother or sister had breast or ovarian cancer. Two other studies failed to find association of breast and prostate cancer (66,67).

The genes *BRCA1* and *BRCA2*, which increase the risk for breast cancer, have been studied for their risk on prostate cancer. *BRCA1* is on chromosome 17q21 and encodes a protein that has been implicated in the regulation of cell cycle progression and various transcriptional pathways. Population-based studies of Ashkenazi Jews have evaluated the two common *BRCA1* founder mutations among this ethnic group, 185delAG and 5382insC. Based on two large epidemiologic studies, the risk of prostate cancer among carriers of these founder mutations appears to be double that of non-carriers, with a cumulative risk of 30% by age 80 (68,69). However, there are no clear prostate cancer histopathologic features portrayed by these mutations (70), Furthermore, because the frequency of these founder mutations is not large, ~2%, it has not been unusual for clinical studies to find that Ashkenazi men with prostate cancer do not carry these *BRCA1* mutations (71–74). The gene *BRCA2*, residing on chromosome 13q12, has provided somewhat consistent evidence that it leads to an increased risk of prostate cancer, with relative risks estimated as high as 5-fold (75) to 7-fold (76), and the evidence points to a more important role for prostate cancer at a young age. Similar to studies of *BRCA1*, clinical studies have found that the mutations of *BRCA2* are rare in men with prostate cancer who have a strong family history of prostate cancer (77). Overall, it appears that men who carry a mutation of either *BRCA1* or *BRCA2* are at a significantly increased risk of prostate cancer, but these mutations are rare and explain only a very small fraction of hereditary prostate cancers.

As a whole, the studies of the familial aggregation of breast and prostate cancers suggest that if there is an association between these types of cancers in families, the association is weak, and likely to be due to multiple genetic and environmental factors. Studies of extremely high risk families, either high risk for breast cancer or high risk for prostate cancer, suggest that some families may have unusually large amounts of aggregation of both cancer types, and that a single gene (e.g. *BRCA2*) may explain some unusual families. But, for the majority of hereditary prostate cancer families, it does not appear that a single gene, nor perhaps a few genes, will be found to explain the aggregation of breast and prostate cancers.

Beyond breast cancer, some studies have suggested that brain/CNS cancers co-aggregate in families with prostate cancer. Studying probands with prostate cancer, Cannon *et al.* (17) found an increased risk for brain/CNS cancers to their relatives (relative risks of 2.7 for sisters and 1.3 for brothers). Isaacs *et al.* (21) also found an elevated risk for CNS cancer, but only among families with hereditary prostate cancer: RR = 3.0 if hereditary prostate cancer, but RR = 0.8 if only familial prostate cancer. The distinction between familial and hereditary prostate cancer was based on the Carter criteria. A study of offspring of Swedish men with prostate cancer did not find significantly elevated risks of brain cancer among their offspring (63). This study, however, was not enriched for hereditary prostate cancer. Some genetic linkage studies have suggested that there may be a susceptibility locus for both brain and prostate cancers on chromosome 1, yet restricted to families with a strong family history of prostate cancer (78). As discussed below, the replication of this finding has not been consistent.

Because the co-occurrence of prostate cancer with other cancers has not been consistent across different studies, some investigators view the genetic susceptibility to prostate cancer to be site-specific for only prostate cancer. Although this may be the case for many prostate cancer families, there remains the possibility that some families may be genetically prone to combinations of multiple cancers, including prostate, breast and brain cancers. Further progress on resolving this will likely await identification of susceptibility genes for prostate cancer, so that well-designed studies can be used to evaluate the likely subtle effects of underlying genes on cancer phenotypes.

SEARCHING FOR GENES BY LINKAGE STUDIES

The search for prostate cancer susceptibility genes by linkage studies offered early hope that finding genes would be as 'easy' as finding genes for breast cancer and colon cancer susceptibilities. An advantage of linkage studies is that the entire genome can be screened in an efficient manner, using genetic markers (usually short tandem repeats) to search for regions that show excessive sharing of inherited alleles among affected men. Over the past 7 years there have been many published reports of suggestive linkage of prostate cancer susceptibility to different chromosomes. These findings have accumulated during the conduct of ongoing linkage studies, often representing snapshots in time of an incomplete accumulation of families, and incomplete genome scans. A chronological summary of these reports is provided, along with efforts to replicate initial 'positive' findings.

Interpretation of the literature on prostate cancer linkage is hampered by loose-adherence to statistical criteria for claiming a positive linkage finding, and for claiming when a linkage finding has been replicated. Many reports summarize linkage results by either multipoint heterogeneity lod scores (*HLOD*) or multipoint model-free *NPL* scores, and some report only two-point LOD scores. The multipoint accounts for all the genetic markers simultaneously, providing more information than separate two-point analyses. The lod score is the probability of the observed data under linkage versus no linkage, on the log-10 scale, and heterogeneity allows for only a fraction of the pedigrees to be linked. The model-free methods do not require an assumed mode of inheritance, penetrance, or allele frequency for the putative susceptibility allele, which can be an advantage for a complex disease such as prostate cancer. However, the *NPL* scores and lod scores are on different scales. To make them comparable for this review, *NPL* scores are converted to lod scores by the equation $NPL - LOD = NPL^2/[2\ln(10)]$. Traditionally, an LOD score of 3 or greater has been considered statistically significant evidence for an initial positive linkage finding (corresponding to a traditional *P*-value of 10^{-4}). Recent emphasis has been placed on higher LOD scores for complex traits, such as an LOD score of 3.3 for pedigree linkage and an LOD score of 3.6 for affected sib-pair allele sharing statistics (79), although debate surrounds the actual cutoff (80,81). For replicating a linkage finding, a *P*-value of 0.01 has been suggested (79), which corresponds to an LOD score of ~1.2. For this review, LOD scores are presented, and initial linkage reports are qualified as significant if LOD scores are at least 3, and replication attempts are qualified as confirmatory if LOD scores are at least 1.2.

The review below summarizes linkage reports for chromosomal regions, and for some of these regions, subsequent studies of candidate genes. Each subsection is denoted by the accepted nomenclature of either the chromosomal region or the candidate gene. It is important to recognize that the studies differ in many ways, such as the ascertainment criteria (e.g. affected sib-pairs versus pedigrees with many affected subjects; hospital-based versus population-based registries), confirmation of prostate cancer (e.g. death certificates, medical records, or family history), methods of analysis (e.g. penetrance models for age-dependent penetrance, model-based versus model-free analyses), and definitions for subset analyses (e.g. age cutoffs for young versus old age of diagnosis). Furthermore, different publications from the same investigators often contain overlapping pedigrees, reflecting the ongoing recruitment of pedigrees. So, some studies from the same investigators cannot be considered as independent replication of earlier results. Ultimately, a pooled analysis of data from genome-wide linkage scans, with standardized definitions for clinical and subset criteria, as well as standardized analytic methods, would greatly facilitate understanding of the linkage results for prostate cancer. More detailed summaries of linkage reports can be found elsewhere (82).

HPC1 region and *RNASEL* gene

Significant linkage to chromosome 1q23–25 was first reported in 1996 among 91 families from North America and Sweden, with a maximum *HLOD* of 5.43 for chromosome 1q23–25, and an estimated 34% of the pedigrees linked to this region (83). This region is now denoted *HPC1*. Although the estimated fraction of linked pedigrees appears impressive, this estimate is likely to be biased (84), as emphasized in a follow-up study of *HPC1* (85). In a subsequent analysis of the same set of families, the strongest evidence for linkage to *HPC1* was found among men with an early age of diagnosis ($HLOD = 4.88$ if age < 66 years; $HLOD = 0.28$ if age ≥ 66 years), and the evidence increased if in addition there were at least five men affected (86). Despite this strong initial evidence, the linkage for *HPC1* has been difficult to replicate with confidence. Two reports found somewhat weak supporting evidence for linkage. One study found an $NPL - LOD$ of 0.54 among 59 families, and slightly stronger evidence among 20 families with hereditary prostate cancer ($NPL - LOD = 0.64$) (87). A second study found an $NPL - LOD$ of 0.19 among 92 families (88). A study of 41 extended pedigrees from Utah, having a total of 440 prostate cancers, found stronger confirmation with an LOD score of 2.43 (89). Another study found much stronger confirmation if Gleason grade was used as a covariate to adjust for differences in grade, with an adjusted LOD score of 3.25 among 254 families (90); no linkage evidence was found if grade was not considered (91). Men with a higher grade provided stronger evidence of linkage for *HPC1*, which is consistent with two other reports that found either higher grade or stage among the families most likely linked to *HPC1* (92,93).

Other studies failed to confirm linkage to *HPC1*, with LOD scores ranging from 0.0 to 0.02. As a whole, the numbers of

families per study were substantial: 47 families (94), 91 families (95), 150 families (96), and 144 families (97). Although the latter study by Berry *et al.* (97) did not find evidence for linkage in the pool of all families, they found some suggestive evidence in a subset of 102 families that showed male-to-male disease transmission—consistent with autosomal dominance—with an *NPL − LOD* score of 0.86. Xu *et al.* (85) expanded collection of families beyond the original set of families reported by Smith *et al.* (83), and the evidence of linkage was maintained; *HLOD* = 2.54, but the 80 new families contributed only an *HLOD* of 0.44. Because of the many conflicting reports on linkage with *HPC1*, the International Collaboration on Prostate Cancer Genetics pooled 772 families from nine international groups (all represented by the prior reports on *HPC1* linkage), and found confirmatory linkage evidence with an *HLOD* of 1.4 (98). The evidence was greater among 491 pedigrees with male-to-male disease transmission, with an *HLOD* = 2.6. In total, there is convincing evidence that *HPC1* is likely to harbor a susceptibility gene for prostate cancer among families with a very early age of onset and a strong family history of this disease. Although the fraction of such families that segregate this gene is unknown, it is likely to be a small fraction.

Because early studies showed linkage of *HPC1* to chromosome 1q24–25, Carpten *et al.* (99) used recombination mapping and candidate gene studies to map several genes to this region, including the gene *RNASEL*. RNase L mediates antiviral and proapoptotic activities of the interferon-inducible 2–5A system, and so is likely to host responses to infections, which may play a role in susceptibility to prostate cancer (100). To identify this gene, index cases from a set of 26 families at high risk for prostate cancer were screened; this set included eight pedigrees linked to *HPC1* and having at least four affected men sharing an *HPC1* haplotype. A nonsense mutation, *Glu265X*, was detected in an index case of European ancestry, and found to be present in all three of his affected brothers (the affected father did not have DNA available). An initiation codon mutation, *Met1Ile*, was detected in an African American index case, and four out of six affected men in this family carried it. Functional studies suggested that both mutations prevent synthesis of functional RNase L. In a follow-up study by Rokman *et al.* (101) of 116 index cases with hereditary prostate cancer, a truncating mutation, *E262X*, was found in five (4.3%) cases; four of these five index cases came from families with at least three men with prostate cancer, suggesting that *E262X* may be most critical for families with a large number of affected men. This was supported by another component of Rokman's study that used a series of 492 Finnish men unselected for prostate cancer, and hence few with a strong family history of prostate cancer, along with 566 healthy male blood donors; no significant difference for carriers of *E262X* was detected, with an OR of 1.15. Another study among 95 men with prostate cancer from 75 families found the *E262X* mutation in one family, with two of three affected brothers heterozygous carriers (102). A total of six missense and nonsense mutations in *RNASEL* were detected in this study, of which five were previously found by Carpten *et al.* (99).

In a separate study of Ashkenazi Jews, a novel frameshift mutation (471delAAAG) in *RNASEL* was detected, which leads to premature truncation of the protein, and was estimated to be as frequent as 4% in this population (103). Using families from the USA, Casey *et al.* (104) evaluated a common missense variant of *RNASEL*, *Arg462Gln.* From 423 cases and 454 sibling controls, it was estimated that heterozygous carriers had an OR of 1.46, and homozygous carriers had an OR of 2.12, giving a population attributable fraction for this variant of 13%. However, another study found an opposite trend, with ORs of 0.83 for heterozygotes and 0.54 for homozygotes (105). Furthermore, a study from Japan based on 101 familial prostate cancers and 105 controls did not find the *Arg462Gln* variant among cases, but found 7.6% of the controls to carry it (106). Nonetheless, this study did find an increased prostate cancer risk for a different *RNASEL* variant, *Asp541Glu*, with an OR of 3.07. In summary, a number of studies provide strong support, both functional and epidemiological, that *RNASEL* plays a role in hereditary prostate cancer, yet other studies have suggested that its role may be small. Further work will be required to sort out the roles of the various variants of the *RNASEL* gene.

PCAP region

Linkage to chromosome 1q42.2–43 was detected in 47 French and German families in 1998, with an *HLOD* of 2.2 (50% families estimated as linked), and with stronger evidence among men diagnosed at age <60 years (*HLOD* = 3.3) (94). The replication of this finding has been difficult. Minimal suggestive evidence was reported among 159 pedigrees, with an *HLOD* of 0.24 (85). A follow-up study that used 64 families, 37 of which were in the initial report by Berthon *et al.* (94), found an *HLOD* of 2.65 (107). When subset to the 27 new families, the maximum two-point LOD score was 0.86, suggesting that most of the evidence for linkage came from the original families. Most other reports found no evidence for linkage: (1) using 230 families alone (91) or combined with 49 new families from Washington University (108); (2) using 94 families in a genome scan (109) or expanded to 152 families to examine linkage with *PCAP* (110); (3) using 144 families (97); (4) using 97 families (111). In spite of this, a reanalysis of 254 families from Washington University found some evidence for linkage to the region of *PCAP* with a LOD score of 2.84, after adjusting for both male-to-male transmission and Gleason grade (without adjustment, the LOD score was 0.32). A likely candidate gene in this region is the Prostate Carcinoma Tumor Antigen-1 (*PCTA-1*). However, based on a screen for deleterious mutations among 77 familial cases from German and French pedigrees, none of the identified sequence variants of *PCTA-1* were likely to be functional, and further evaluations suggested that it is not likely to play a major role in hereditary prostate cancer (112).

HPCX region

Significant linkage to chromosome Xq27–28 was detected in 360 families from four groups representing North America, Finland, and Sweden (113). The maximum *HLOD* was 3.85, with an estimated 16% of the families linked. Because X-linked inheritance implies transmission of a susceptibility allele from mothers to sons, but not from fathers to sons, families were stratified according to male-to-male (M–M) inheritance of

prostate cancer. Consistent with this logic, the 129 families without M–M inheritance provided stronger linkage evidence (*HLOD* = 2.46) than the 190 families with M–M inheritance (*HLOD* = 1.47). See Schleutker *et al.* (114) for further analysis of the Finnish families. A number of studies have provided some supporting evidence of linkage to *HPCX*, to varying degrees of confidence. Among 153 families, Lange *et al.* (115) found a two-point *NPL − LOD* of 0.24, although, contrary to expectation, the evidence was stronger among the 43 families with M–M transmission (two-point *NPL − LOD* = 0.78) than among the 110 families without M–M transmission (two-point *NPL–LOD* = 0.17). After sub-setting the families without M–M transmission to early age of diagnosis, the *NPL − LOD* increased to 0.50. In a genome-wide scan of 98 families, Hsieh *et al.* (116) found confirmatory linkage with an *NPL − LOD* of 1.43. Among 104 German families, Bochum *et al.* (117) found an *HLOD* of 0.72, although, contrary to expectation, the linkage evidence was greater among the 41 families with M–M transmission (*HLOD* = 0.93) than among the 63 families without M–M transmission (*HLOD* = 0.08). If there is a susceptibility locus on the X-chromosome, there must be a large amount of error when attempting to use family history to classify pedigrees as likely segregating an X-linked mutation. Among 186 families, Peters *et al.* (118) found a maximum two-point LOD score of 0.63, and this increased to 1.14 among the subset of 23 families without M–M transmission. Among 254 families, Goddard *et al.* (90) found an LOD score of 3.06, after adjusting for Gleason grade (without adjustment, the LOD score was 0.26). Although the androgen receptor gene may play a role in prostate cancer, it is not likely to be the *HPCX* susceptibility gene, because these two loci are separated by more than 50 cm. To date, no prostate cancer susceptibility genes have been identified in the *HPCX* region.

CAPB region

Because epidemiologic studies have suggested a familial association between prostate and brain cancers, and loss of heterozygosity has been frequently observed in tumors of the brain and CNS, Gibbs *et al.* (78) screened for linkage in a subset of 12 families with a history of both prostate and primary brain cancers. A maximum two-point LOD score of 3.22 on chromosome 1p36 was found, which increased to 3.65 in the subset of six families with an average age of prostate cancer diagnosis <66 years. This finding has not been convincingly replicated. In a follow-up study by the same group of investigators, the strongest evidence for linkage among 21 families with primary brain cancer was on chromosome 6 (HLOD = 2.34), but still with some evidence for linkage to chromosome 1 (HLOD = 1.75) (119). Among nine families from the UK with both prostate and brain cancers, an *HLOD* of 0.07 was found, which increased to 0.48 among five families with an average age of prostate cancer diagnosis <66 years (120). Xu *et al.* (85) found stronger confirmatory evidence among 12 families with a history of prostate cancer and primary brain cancer, with a two-point LOD score of 3.22. Two other studies found no evidence for linkage, with all LOD scores negative in a set of six families (107), and in another set of 13 families (97). In summary, the most consistent linkage for *CAPB* has been within families with a strong family history of prostate cancer and a young age of prostate cancer diagnosis. These observations highlight the importance of collecting and confirming information on other cancers among family members. A major hurdle to confirm the linkage of *CAPB* is the few families that have both prostate and brain cancers.

HPC20 region

In 2000, Berry *et al.* (121) reported suggestive linkage for chromosome 20q13. Among 162 families, using an assumed dominant model, an *HLOD* of 1.08 was found, and using an assumed recessive model, an *HLOD* of 2.94 was found. The linkage evidence was strongest among families with an average age of diagnosis ≥65 years, less than five men affected, and no M–M disease transmission. Interestingly, these results are consistent with segregation results from Cui *et al.* (42), which suggested that for older-onset disease, a recessive model is more likely. Among 159 families, Zheng *et al.* (122) found somewhat consistent results, with a maximum *HLOD* of 0.08 for a dominant model and an *HLOD* of 0.42 for a recessive model, with the strongest evidence in the same types of families as those found by Berry *et al.* (121). In another study of 172 families, Bock *et al.* (123) found an *HLOD* of 0.08, with stronger evidence provided by a subset of 16 African American families (*HLOD* = 0.86). In another study of 66 families, *HLOD*s of 0.03–0.11 were found, depending on the assumed penetrance (124). Interestingly, the four genes *CSEIL*, *ZNF217*, *MYBL2*, and *STK15* within 20q13 have been shown to be over-expressed in prostate cancer, and two of these (*MYBL2* and *STK15*) are overexpressed in prostate metastases (125). However, linkage to *HPC20* has yet to be confirmed, and no susceptibility genes in this region have been identified.

8p22–23 region and *MSR1* gene

In 2001, Xu *et al.* (126) reported suggestive linkage to chromosome 8p22–23 among 159 families, with an *HLOD* of 1.84. This was an exciting finding, because this region is frequently found to have loss of heterozygosity in prostate cancer tumors. Linkage to 8p22–23 was supported in an independent study of 57 families from Sweden (*HLOD* = 1.08) (127). Results from subset analyses, however, were opposite from those of Xu *et al.*: Xu *et al.* (126) found strongest evidence for linkage in families with an average age of diagnosis ≥65 years and a larger number of men affected, yet Wiklund *et al.* (127) found stronger evidence in families with younger age of diagnosis and fewer number of affected men. In a mutation screening study of hereditary prostate cancer families, six rare missense mutations and one nonsense mutation were detected in the macrophage scavenger receptor 1 gene (*MSR1*), and these were found to co-segregate with prostate cancer (128). The *MSR1* gene encodes proteins that function with host responses to infections, which may play a role in susceptibility to prostate cancer (100). In a follow-up study of 301 non-hereditary prostate cancer cases and 250 controls, five common variants within *MSR1* were found, with statistically significant differences in allele frequencies (129). One of the largest differences was for a SNP in the promoter region, with allele frequencies of 7.6% among controls and 12.3% among cases. In contrast, Wang *et al.* (130) could not

detect an association of *MSR1* variants with prostate cancer, using 438 familial cases, 499 sporadic cases, and 493 controls. A nonsense mutation (*R293X*) was detected, but its allele frequency was highest among controls (3.25%) compared with the familial (1.64%) and sporadic (2.82%) groups. Another study of similar size from Finland also found no significant associations (131). Understanding the role of *MSR1* will require more thorough evaluations and replication.

HPC2 region and *ELAC2* gene

In 2001, Tavtigian *et al.* (132) reported significant linkage to chromosome 17p based on 33 pedigrees with a multipoint LOD score of 4.3. Positional cloning and mutation screening lead to detection of a gene, *ELAC2*, that harbored mutations that segregated with prostate cancer in two pedigrees. Two common missense variants, *Ser217Leu* and *Ala541Thr*, were also found to be associated with prostate cancer. At about the same time, Rebbeck *et al.* (133) found that men who carried both *Leu217* and *Thr541* variants were at an increased risk of prostate cancer, with an OR of 2.37. In contrast, in a linkage study of six markers around the *HPC2* locus, Xu *et al.* (134) found no evidence for linkage using 159 families, even after exploring subsets of pedigrees according to age of prostate cancer diagnosis, number of affected men, or race. Rokman *et al.* (135) screened for mutations of the *ELAC2* gene in 66 prostate cancer families from Finland, but no truncating mutations were found. From this same study, no associations of *Leu217* or *Thr541* were found using 107 hereditary and 467 unselected prostate cancer cases, and 568 controls. Shortly after these initial reports, a number of contradictory association studies were published, with varying criteria for selection of cases and controls. A meta-analysis by Camp and Tavtigian (136) of six studies (132–134,137–139) published until July 2002 estimated a summary OR of 2.4 when comparing familial cases versus controls, and a reduced OR of 1.3 when comparing all cases (familial and sporadic) to controls. A subsequent large Australian population-based study of 825 cases and 732 controls found no association of *Leu217* or *Thr541* with prostate cancer (140). Their meta-analysis, which added their data to the study of Rokman (135) and the six studies from Camp's meta-analysis, estimated summary ORs of 1.04 for *Leu217* homozygotes and 1.18 for carriers of *Thr541.* These risks did not differ significantly from 1, so it was concluded that there is no evidence of associations of *ELAC2* polymorphisms with prostate cancer. However, this study was dominated by sporadic prostate cancers, so it is still possible that *ELAC2* may play a role, albeit a relatively small role, in hereditary prostate cancer. In another large population-based study of 591 cases and 538 controls from the USA, published after the meta-analyses, a statistically elevated OR of 1.84 was found for *Leu217* homozygotes, but no association was found for the *Thr541* variant (141). Other studies published after the meta-analyses have been inconsistent. A study of 199 cases and 525 controls from Canada found that carriers of *Leu217* were at an elevated risk, with OR = 1.6 (but not when considering only homozygotes for *Leu217*), and that carriers of *Thr541* had an increased risk for late-onset prostate cancer (142). In a study of 432 cases and 469 controls from the UK, no association was found for *Thr541*, but the *Leu217* variant was not evaluated (143). Among 119 cases and 223 controls, all Afro-Caribbean from Tobago, no significant associations were found for either variant (144). Three recent studies from Japan gave inconsistent results. Among 350 cases and 356 controls, both *Leu217* and *Thr541* variants were statistically more frequent among cases than controls (145). The second study of 98 sporadic cases and 255 controls found an association with the *Leu217* variant (OR = 3.11); no subjects had the *Thr541* variant (146). The third study used 81 cases with a family history of prostate cancer and 106 controls, and found no association of either variant with prostate cancer (147). A limitation of these studies from Japan is that the *Leu217* and *Thr541* variants are less frequent among Japanese than among Caucasians, which implies weaker power to detect associations. Overall, it appears that if *HPC2/ELAC2* plays a role in prostate cancer, it is a weak role for most forms of prostate cancer.

Genome-wide linkage scans

Recently, a number of studies have completed their planned genome-wide linkage scans, and these are summarized in Table 3. Two earlier published linkage scans are not presented in Table 3 (83,109), because they are now superseded by subsequent studies presented in this table. Two different types of analyses are presented for the study by Suarez *et al.* (91)—those presented in the initial report, and those from a subsequent analysis by Goddard *et al.* (90) based on the same set of families, but using a different statistical method that allowed adjustment for covariates. Eight of the studies in Table 3 were published in the same journal (*Prostate*), along with a summary (148). The evidence for linkage to each chromosome is summarized as a score of 1, 2 or 3, corresponding to a maximum LOD score on the chromosome within the ranges of 1–2, 2–3, or >3. To evaluate whether there is consistent evidence for linkage, a minimal LOD score of 1 was used. The last column of Table 3 gives a count of the number of studies with an LOD score of at least 1. Three chromosomes, 4, 6 and 7, had LOD scores of at least 1 across five independent studies. The analyses by Goddard *et al.* (90) provide many more large LOD scores than any other study, and so further use of their analytic methods across different studies is warranted to determine if their results can be reproduced. If we ignore the analyses of Goddard *et al.*, two chromosomes, 11 and 16, have LOD scores of at least 2 for two independent studies. Interestingly, chromosome 16 was initially detected, and replicated, among two independent studies that sampled affected sib-pairs, which differs from the other studies that tended to require a family history of at least three men with prostate cancer. Table 3 illustrates the extreme difficulty in finding consistent linkage results across different studies. A limitation of this presentation is that it summarizes linkage findings in the total of each set of families. Given the large amount of heterogeneity of prostate cancer, subset analyses are warranted, such as by age of diagnosis, amount of family history, severity of disease, etc. However, such an analysis would require a pooled analysis with consistent definitions across studies, and more stringent cutoffs for claiming positive linkage results, to avoid the increased chance of false-positive findings from analyzing multiple subsets.

Table 3. Summary of genome-wide screens for prostate cancer susceptibility loci. For each chromosome, 1, 2 and 3 are ranges for LOD scores of 1–2, 2–3, and >3. LOD scores are either *HLOD*s or *NPL − LOD*s

Author	Suarez, 2000 (91)	Goddard, 2001 (90)	Witte, 2003 (153)	Hsieh, 2001 (116)	Cunningham, 2003 (182)	Edwards, 2003 (183)	Janer, 2003 (119)	Lange, 2003 (184)	Schleutker, 2003 (185)	Wiklund, 2003 (186)	Xu, 2003 (187)	No. studies with LOD > 1
No. families	230		124	98	160	64	254	175	13	50	188	
Population	USA		USA	Canada USA	USA	Australia Canada Texas Norway UK	USA	USA	Finland	Sweden	USA	
Chromosome												
1		3									1	2
2	1	3				1					2	3
3		3				1			2		1	4
4		2				1		1		1	2	5
5		2				1		1		1		4
6		1			1	1	2				1	5
7		1					2	1		1	1	5
8		2					1				1	3
9								1			2	2
10											1	1
11			2			1	1		3			4
12	1	2		1								2
13												0
14		2										1
15	1	2						1				2
16	2	2	2									2
17								2				1
18						1					1	2
19				1						2		2
20		1			3						1	3
21		3										1
22												0
X		3			1						1	3

Linkage with prostate cancer aggressiveness

In contrast to the above linkage analyses that focused on susceptibility to prostate cancer, Witte *et al.* (149) screened for linkage with Gleason's grade of prostate cancer. Gleason's grade is a measure of prostate tumor differentiation, ranging from 2 to 10, and is considered to measure aggressiveness of the disease. Analyzing Gleason grade as a quantitative trait differs from treating it as a stratification factor to assess linkage heterogeneity. For linkage with a quantitative trait, it is expected that men who share similar Gleason grade (e.g. a pair of brothers with both low scores, or both high scores) also share inherited regions of the genome, as indirectly measured via the genetic markers. For linkage heterogeneity, it is assumed that some subsets are not linked (e.g. low Gleason grade) and that some subsets are linked (e.g. high Gleason grade). Using Gleason grade as a quantitative trait, Witte *et al.* analyzed 513 affected men from 233 families and found evidence for linkage on several chromosomes. Although they report their findings by *P*-values, these are converted to LOD scores for this review ($\text{LOD} = \chi^2_{1,1-2p}\log_{10}(e)/2$, where $\chi^2_{1,1-2p}$ is the quantile of a chi-square distribution with one degree of freedom, at the percentile $1 - 2p$, p is the *P*-value, and e is the base of the natural logarithm). They found LOD scores of 2.7 for chromosome 5q31–33, 2.4 for chromosome 19q12, and 2.2 for chromosome 7q32 (149). Further fine-mapping and loss of heterozygosity in prostate tumors helped to refine regions on chromosomes 7 and 19 (150,151). An independent study of 364 men from 161 families confirmed linkage of Gleason's grade with chromosome 19q (LOD = 3.9), provided supportive linkage evidence for chromosome 5 (LOD = 1.4), but found no linkage for chromosome 7 (152). In addition, chromosomes 4 and 15 were found to have suggestive linkage (LOD scores of 2.9 and 1.9, respectively). In a second independent replicate sample of 259 men from 114 families, Witte *et al.* (153) found supportive linkage for chromosomes 7q32 (LOD = 2.1), 5p15 (LOD = 1.6), and 9q34 (LOD = 1.2). Another study from Germany confirmed linkage of chromosome 7 with aggressiveness of prostate cancer, but used the American Joint Committee on Cancer grade I–IV, because Gleason grade was not frequently used (154). Instead of analyzing aggressiveness as a quantitative trait, they essentially subset their families to those with at least two men with grade III disease. Among 10 families with high-grade disease, the LOD score was 1.4 for 7q31–33. All of these studies suggest that prostate cancer aggressiveness may be modified by several genes. It is somewhat surprising that there is sufficient power to detect linkage with Gleason grade, because although it can range from 2 to 10, the majority of men have scores of 5–7 [75% in the study by Witte *et al.* (149), and 78% in the study by Slager *et al.* (152)]. Furthermore, the increase of disease aggressiveness is smaller when changing from a score of 5–6, than from a score of 6–7. Despite this narrow range in actual scores, linkage with Gleason grade has been strongly supported for some chromosomes. Future work may benefit by using additional clinical information in order to better discriminate, on a broader quantitative scale, the entire spectrum of disease aggression. It is important to recognize that some of the chromosomes found linked to Gleason grade have only weak evidence for linkage to prostate cancer susceptibility (e.g. chromosomes 5 and 19), which suggests that genes that influence susceptibility to prostate cancer may differ from those that influence the aggressiveness of disease after it has occurred. Refined use of clinical information and statistical methods may help to distinguish between genes that influence the entire spectrum of disease aggressiveness, versus genes that influence disease susceptibility in only a subset of the most aggressive cancers (155).

COMMON GENETIC POLYMORPHISMS

In contrast to the above family-based approaches to identify the rare moderate-to-high penetrant susceptibility genes, a large number of studies have focused on more common genetic polymorphisms that are likely to have small relative risks, yet large population attributable risks due to their higher frequencies in populations. Given the difficulty in reproducing linkage studies for the presumably high penetrant genes, it may be worthwhile to consider whether common genetic polymorphisms might play a role in the modulation of genes related to hereditary prostate cancer. This is purely speculative at this point, but all evidence seems to point towards the effects of multiple genes involved in the risk for prostate cancer.

The most likely candidate genes are those involved in the metabolism of testosterone and other androgens, because the growth of prostatic cells depends on testosterone. Genes that encode products that likely play a critical role inducing androgen stimulation of the prostate are: (1) the androgen receptor (*AR*) gene, located on chromosome Xq11–12, which encodes the androgen receptor that is involved in androgen binding and transport; (2) the steroid 5-α-reductase type II (*SRD5A2*) gene, located on chromosome 2p23, whose enzyme product converts testosterone to the more potent androgen dihydrotestoserone; (3) the cytochrome p450c17α (*CYP17*) gene, located on chromosome 10q24.3, whose enzyme product regulates steps in testosterone biosynthesis; and (4) two genes of the *HSD3B* gene family, located on chromosome 1p13.13, which encode 3beta-hydroxysteroid dehydrogenases that are involved in metabolism of dihydrotestoserone in the prostate, as well as catalysis of testoserone biosynthesis. These genes have been extensively studied and reviewed elsewhere (156,157). Like many other candidate gene studies of prostate cancer, associations of these four genes with prostate cancer have been difficult to replicate in a consistent manner. For example, a recent meta-analysis of the *SRD5A2* gene concluded that the *V89L* allele was not associated with prostate cancer, and that the *A49T* and *TA* repeat alleles may have a modest effect, but bias and chance findings could not be excluded (158). Another meta-analysis of the *CYP17* gene suggested that it is not likely to increase the risk of prostate cancer for men of European descent, although it may increase risk for men of African descent (159). For the *AR* gene, a large number of studies have evaluated the risk associated with the number of microsatellite repeats of *CAG* and *CGN* in exon 1 of the *AR* gene. Longer *AR* variants have decreased transcriptional activity and decreased binding affinity for androgens, and so may offer protection from prostate cancer, whereas shorter variants may increase prostate cancer risk. This in fact has been observed in some studies, but not all. See Coughlin and Hall

(157) for a thorough review. For the *HSD3B* genes, a weak association of prostate cancer with the *HSD3B1* gene was found, and stronger association was found when the joint effect of the two genes *HSD3B1* and *HSD3B2* was considered, especially for hereditary prostate cancer (160). Because fewer studies have focused on the *HSD3B* genes, more work is required to understand their potential roles in prostate cancer.

Besides genes involved with androgen metabolism, a number of studies have evaluated genes involved in the metabolism of environmental carcinogens (such as *CYP2D6*, *CYP2C19*, *GSTM1*, *GSTP1*, *GSTT1*, *NAT1* and *NAT2*), the vitamin D receptor (*VDR*), and the gene that encodes PSA—*KLK2*. For a review of these genes, see Coughlin and Hall (157) and Rebbeck (161). Many of the studied genes have strong biological support, yet consistent and replicable prostate cancer risks associated with these candidate genes have not been achieved.

DIETARY AND ENVIRONMENTAL RISK FACTORS

A large number of studies have evaluated the risk of dietary and environmental exposures on the risk of prostate cancer, yet with mixed findings. These are briefly reviewed to illustrate that non-genetic risk factors have been as difficult to replicate as genetic risk factors. Given that dietary and behavioral risks are likely to cluster within families, discriminating genetic from non-genetic risks will be particularly challenging, yet likely critical since the magnitude of risk is about the same for both genetic and non-genetic risk factors.

A substantial number of studies have reported positive associations of total or saturated animal fat with prostate cancer, yet other reports have failed to replicate these findings. The consumption of red meat has demonstrated more consistent positive associations with prostate cancer than studies on fat, with risk ratios tending to be at least 1.3. Although the components of red meat that promote the development of prostate cancer are not known, several hypotheses have been posed: (1) red meat is a major source of zinc, which is essential for testosterone synthesis, and high levels of testosterone increase the risk of prostate cancer (although conflicting studies have suggested that zinc may protect against prostate cancer) (162); (2) cooking meats at high temperatures, or on charcoal grills, causes the formation of carcinogens in the form of heterocyclic aromatic amines and polycyclic aromatic hydrocarbons; (3) diets high in meat may be deficient in anticarcinogenic constituents found primarily in plant foods. For a review on the risk of fat and meat consumption, see Kolonel (163). The role of fruit and vegetables has not been consistent, although there is a trend for studies suggesting that vegetables (including tomatoes, legumes, and beans) tend to decrease the risk of prostate cancer; for a review, see Chan and Giovannucci (164). High intake of tomatoes, which contain the antioxidant carotenoid lycopene, has been associated with reduced risk of prostate cancer (165). Vitamin E and selenium, which are also antioxidants, may also reduce the risk of prostate cancer (162,166–168). Vitamin D has been suggested to reduce the risk of prostate cancer, and 1,25 dihydoxyvitamin D_3 (1,25 D) a vitamin D metabolite, consistently inhibits prostate cancer cell growth and development. Epidemiologic studies have suggested that dairy calcium may increase the risk of prostate cancer, which may occur because calcium intake can suppress circulating 1,25 D levels. However, the large body of literature on vitamin D has been mixed with positive and negative findings (169).

The association of prostate cancer with behavioral risk factors have been evaluated in a large number of case–control studies. The results for risk factors such as physical activity,z sexual activity, and use of tobacco and alcohol have generally indicated that these factors can be ruled out, at least by the crude methods of measuring these behaviors (reviewed in 170,171). A large number of studies has evaluated the risk of various occupations for prostate cancer. Although no occupation, or particular occupational exposure, has provided persuasive evidence, three meta analyses reported a slightly increased and statistically significant risk conferred by farming, with summary relative risks on the order of 1.1. Although pesticides and herbicides are likely candidates, studies of them have not provided consistent results (172), and most studies have not measured exposure at the individual-level. Other confounding risk factors, such as diet and physical activity, complicate the evaluation of farming risk.

CONCLUSIONS AND FUTURE DIRECTIONS

A large body of evidence supports the view that genetics plays a critical role in prostate cancer susceptibility, yet there are likely to be multiple genes with small to moderate risks. Some families may be segregating a gene with high penetrance, but these families are quite rare. To increase the ability to detect linkage for common complex diseases, a successful strategy has been to study subsets of families that have Mendelian transmission of the disease. This strategy was successful for finding the *BRCA1* and *BRCA2* susceptibility loci for breast cancer, mainly because the families that carried these genes had a much earlier age of onset, some 20 years younger than average. For prostate cancer, use of age of diagnosis to create Mendelian subsets has been challenging, because the mean age of diagnosis for families that look hereditary is only about 6–7 years younger than the non-hereditary forms of disease. To date, there have been no clear clinical features that discriminate hereditary versus non-hereditary forms of prostate cancer. Perhaps reconsidering the definition of 'hereditary' prostate cancer would help, given the recent studies that suggest that X-linked or autosomal recessive components may have a role. Also, more careful use of clinical information on disease aggressiveness may help, given the reproducible linkage findings for Gleason grade. Furthermore, careful consideration of how prostate cancer diagnosis was determined may help, in order to separate men with clinical symptoms versus those identified solely by an elevated PSA. Critical insights may be gained from the study of the genetics of prostate cancer in more homogeneous groups, such as African American men (173).

The linkage findings for prostate cancer have given high hopes, and confusion. Fine-mapping promising regions have lead to important clues, such as the *ELAC2*, *RNASEL* and *MSR1* genes. Conflicting reports of the effects of these genes, and failure to replicate other linkage regions, clouds the

understanding of the genetics of prostate cancer. A particular challenge for linkage studies of prostate cancer is the late age of diagnosis, so DNA is primarily collected for men of a single generation, mainly siblings and cousins. It is possible to infer the missing genotypes of earlier generations, in fact for any deceased man who had prostate cancer, by collecting DNA on any available spouse and offspring. Although this strategy increases the linkage information, it increases the cost and time of a study, and not all studies have gone to this effort. Another complication is verifying prostate cancer diagnoses for deceased relatives. Death certificates are sometimes used, but their availability varies across the different states in the USA. Medical records are sometimes used, but their availability also differs, particularly for men diagnosed decades earlier. Other complications are the high rate of phenocopies, and changing diagnostic criteria, mainly through increasing use of PSA-screening.

The inability to replicate linkage findings, as well as association studies, has been a trademark of most common complex diseases, and discussed broadly in the literature. Some reasons why linkage studies are difficult to replicate are: (1) differences in how families are ascertained [e.g. affected sib pairs, versus large pedigrees with many affected (174)]; unselected prostate cancers versus selection favoring young age of diagnosis, or favoring clinically symptomatic disease; (2) differences in linkage information content (e.g. number of families, size of families, number of genotyped family members and their relationships); (3) differences in laboratory quality of genotypes—undetected genotype errors can dramatically influence linkage results (175); (4) differences in statistical analytic methods (e.g. model-based can be influenced by different penetrances and mode of transmission, and model-free can be influenced by different marker allele frequencies); (5) population differences in susceptibility loci; (6) locus heterogeneity (i.e. different linked loci in different families); and (7) statistical fluctuations. This latter statistical issue can arise simply because the initial report is a false-positive finding. The chance of a false-positive result increases with the number of statistical tests performed on different subsets, or on different definitions of 'affected'. However, even if the initial report is a true-positive, it too can be difficult to replicate due to statistical fluctuations. Typically, the first extreme LOD score value leads to claims of a positive finding, but subsequent attempts to replicate linkage to a given region tend to regress toward smaller LOD scores. In some sense, this is like tracking your blood pressure. Sometimes it is high, which raises concerns, but when tracked over time, the extreme high and low values tend to regress toward the mean value. This statistical fluctuation for linkage studies is magnified when there are multiple susceptibility loci. For example, if a disease is caused by K independent susceptibility loci of approximately equal effects, then the first linkage study will report a positive linkage finding if *any* of these K loci provide a large lod score. By statistical chance, the linkage signal for one of the loci may be much larger than all other loci in a given study. An independent replication study, however, would focus only on the one 'positive' region, and in an independent set of families, the linkage signal is not likely to be as extreme as in the first report. To overcome this statistical regression to the mean, Suarez *et al.* (176) have shown, by simulation experiments, that the sample size required to replicate an initial positive linkage finding should be much larger than the sample size of the initial study. For K loci of equal effects, they showed that the sample size for the replicate study should be $(K - 1)$ times larger than the initial study (176). Although this level of rigor has not yet been achieved for most of the published linkage reports, future efforts by the International Collaboration of Prostate Cancer Genetics may move replication efforts forward by pooled analyses of a large number of pedigrees collected throughout the world, as has been done for the pooled analysis of *HPC1* (98).

A limitation of linkage studies is their weak power to find susceptibility genes of small to moderate effects. An alternative is genome-wide association studies, which tend to have greater power to detect genes of small risk (177). Careful choice of single nucleotide polymorphisms (SNPs) within candidate genes (178) may provide the most powerful method to find relatively common genes of small risk. However, association studies have a limitation that linkage studies do not have. When studying a candidate gene by association, it is difficult to decide when to conclude that the gene *does not* have a role in prostate cancer. Finding no association of multiple variants within a gene does not rule the gene out, because there could still be other unmeasured variants of the gene that increase prostate cancer risk. Linkage overcomes this, because it simply uses co-segregation of genomic regions with disease. A compromise between the two strategies is a hybrid use of both linkage and association in order to screen for shared haplotypes both within and between families. Selection of haplotype-tagged SNPs for genome-wide haplotype associations, as currently being developed by the HapMap project (179), is anticipated to capture genomic information in the form of haplotype blocks. If all alleles within a haplotype block are highly correlated among themselves (i.e. the tagged SNPs as well as the causative susceptibility allele), then the block should capture sufficient information to fully interrogate a particular region of the genome, allowing one to detect an association with an economy of scale, and also allowing one to rule out the role of a region if no significant association is detected. It remains to be shown how well this approach will work for common complex diseases, but it does offer a new future research direction for studying the genetic basis of prostate cancer.

Given the large body of evidence that prostate cancer is likely to have a strong genetic basis, and given the difficulty of finding inherited susceptibility genes, the evidence that prostate cancer is likely to be caused by multiple genes, possibly interacting in complex manners, and possibly interacting with environmental factors, continues to grow. Furthermore, it is certainly possible that the common polymorphisms involved in androgen metabolism, and perhaps those involved in metabolism of environmental carcinogens, might modulate the effects of the higher-risk susceptibility genes responsible for hereditary prostate cancer. Unfortunately, most studies of candidate genes tend to focus on one gene at a time. Future studies of candidate genes, whether for sporadic or hereditary forms of prostate cancer, may need to consider the simultaneous effects of multiple genes. To do so would require much larger sample sizes, particularly if the effect of each gene tends to be small, and even more so if interactions among genes exists. This may require the efforts of larger collaborative groups, with stringent

criteria for disease diagnosis, and collection of pertinent epidemiological and clinical information. Furthermore, more sophisticated statistical modeling of complex genetic pathways may be required to decipher the interrelated effects of each gene (180). In addition, more innovative study designs and genomic methodologies may be necessary. For example, identification of genes that play a major role in regulating other genes may require the measurement of the expression of many genes in prostate cancer tissues, and then use of the amount of gene expression as a quantitative trait for genome-wide linkage studies. This approach has shown promise to map metabolism genes related to obesity in a mouse model (181). Because the availability of fresh tissues among affected family members may be limiting, as well as the costs of gene expression experiments, novel study designs that attempt to maximize the amount of information per family will be crucial.

Our understanding of the complexities of prostate cancer genetics has grown, with many suggestions of promising leads. Studies of common polymorphisms of genes related to the metabolism and biosynthesis of androgens and other steroids have provided a biological foundation for future research. Our understanding of the genes related to hereditary forms of prostate cancer is clearly in its infancy, and the challenge will be to detect genes of small to moderate effects. Future efforts will require more critical use of clinical information, careful study designs that make use of biological markers of disease aggressiveness, larger studies that facilitate creation of homogeneous subsets, and advances in statistical methods to amplify the signals from susceptibility genes in the presence of a variety of heterogeneous factors. We have clearly just begun to understand some of the complexities, and we can only hope that Aristotle was correct when he said that 'Well begun is half done' (Aristotle, 384–322 BC, *Politics*, quoting a proverb).

ACKNOWLEDGEMENTS

Supplemental data for Table 2 was kindly provided by Dr William Page. Encouragement and support from my father, Arnold R. Schaid, are graciously honored. This review was supported by the US Public Health Service, National Institutes of Health (CA72818; CA15083; CA89600; CA91956; GM67768).

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