The Clinical Genetics of Prostate Cancer

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Abstract

Prostate cancer is the most common cancer in men and the second highest cause of cancer-related mortality in the U.K. A genetic component in predisposition to prostate cancer has been recognized for decades. One of the strongest epidemiological risk factors for prostate cancer is a positive family history. The hunt for the genes that predispose to prostate cancer in families has been the focus of many research groups worldwide for the past 10 years. Both epidemiological and twin studies support a role for genetic predisposition to prostate cancer. Familial cancer loci have been found, but the genes that cause familial prostate cancer remain largely elusive. Unravelling the genetics of prostate cancer is challenging and is likely to involve the analysis of numerous predisposition genes. Current evidence supports the hypothesis that excess familial risk of prostate cancer could be due to the inheritance of multiple moderate-risk genetic variants. Although research on hereditary prostate cancer has improved our knowledge of the genetic aetiology of the disease, a lot of questions still remain unanswered.

This article explores the current evidence that there is a genetic component to the aetiology of prostate cancer and attempts to put into context the diverse findings that have been shown to be possibly associated with the development of hereditary prostate cancer. Linkage searches over the last decade are summarised. It explores issues as to why understanding the genetics of prostate cancer has been so difficult and why despite this, it is still a major focus of research. Finally, current and future management strategies of men with Hereditary Prostate Cancer (HPC) are discussed.

Introduction

Prostate cancer is the most common cancer in men and the second highest cause of cancer-related mortality in the U.K. Family history is the strongest risk factor for prostate cancer. A man with one close relative (such as a father or a brother) with prostate cancer has twice the risk of developing prostate cancer as a man with no family history. If two close male relatives (such as a brother and a father) are affected, a man’s lifetime risk of developing prostate cancer is increased fivefold. The degree of relative risk and the increase in its magnitude can be explained by a genetic effect in, at least, a component of the predisposing factors to this disease. It is now becoming clear that the identification of mutations in candidate prostate cancer predisposition genes is proving more difficult to be made than the identification of susceptibility genes for some other common cancers such as breast, ovary, and colon cancer.
This difficulty of prostate cancer predisposition gene identification could be for several reasons. Firstly, prostate cancer is diagnosed at a late age, thus often making it impossible to obtain DNA samples from living affected men for more than one generation. This makes linkage in large pedigrees difficult. Secondly, the presence within high-risk pedigrees of phenocopies (those with prostate cancer, but without the genetic alteration) weakens the linkage results. Finally, the genetic heterogeneity of this complex disease (the fact that different pedigrees may be due to different genes) and the uncertainty of the optimal genetic model could result in inaccurate linkage results which make gene identification difficult.

Significant linkage in familial prostate cancer was first published in 1996. A group from Johns Hopkins University, USA [1] reported linkage at a locus on chromosome 1q24-25, which was named Hereditary Prostate Cancer 1 (HPC1). Since then, several large linkage studies have been conducted, and the results of many different groups have revealed new loci and linkage studies have been conducted, and the results of many different groups have revealed new loci and the uncertainty of the optimal genetic model could result in inaccurate linkage results which make gene identification difficult.

Current body of evidence for the genetic aetiology of prostate cancer

Epidemiological evidence

In the 1950-60s, it was observed that the risk of prostate cancer in relatives of sufferers was higher [7, 8]. Large families have been observed in which prostate cancers seemed to cluster. Early observations were made in large families collected and studied in Utah [9, 10]. To explore the evidence of a familial component, case control, cohort and twin studies have been reported.

Case-control studies

The case-control studies can be split into two simple types. The first type compares prostate cancer incidence in first-degree relatives of prostate cancer patients (cases) with the incidence in relatives of cancer-free individuals (controls). The second type compares the percentage of prostate cancer cases vs. controls with a positive family history of the disease [7-9, 11-26]. These studies indicated that the relative risks (RR) amongst first-degree relatives of affected individuals range from 0.64 to 11.00-fold [27-29]. With the exception of the RR of 0.64 [11], in a study which was done on a small sample set of 39 families, 15 of these 16 studies reported a RR of 1.76 or higher. The RR increases further when more than one relative is affected. Steinberg et al, 1990, [15] showed that the RR with an affected first-degree relative was 2.0, with a second-degree relative was 1.7, but with both first- and second-degree relatives combined, RR rose markedly, to 8.8. In addition to this, they observed that the RR increased as the number of family members increased, with RRs of 2.2, 4.9 and 10.9 for 1, 2 and 3 additional affected relatives besides the proband, respectively [15]. This is all strong evidence for the involvement of a genetic component in familial disease as these increases in RR are too large to be accounted for solely by an environmental effect. Further evidence of a genetic effect is shown by the observation that the RR to relatives increases as the age of the proband decreases [9, 30]. A brother of a proband with prostate cancer at the age of 50 has a 1.9-fold higher risk of developing prostate cancer compared with a brother of a man diagnosed with the disease at the age of 70 [30].

Cohort studies

Cohort studies attempt to avoid possible bias by focussing on an unselected population. Goldgar et al [31] showed a familial prostate cancer RR of 2.21 in first-degree relatives of 6,350 probands from an unselected population from the Utah Population Database. Similarly Gronberg et al [32] found an RR of 1.70 from their study involving 5,496 sons of Swedish men from Cancer Registry data.

Twin studies

These show that there is an increased RR in mono-compared with di-zygotic twins of just over 3- to 6-fold [33]. Page et al [34] studied 15,924 male twin pairs and found pair wise concordance (twin pairs where both men were affected) rates amongst monozygotic twins was 15.7% whilst for dizygotic twins the frequency was
3.7% (p =< 0.001). Proband wise concordance (number of concordant affected twins divided by total no of affected twins) was 27.1% for monozygotic twins and 7.1% for dizygotic twins, which gives a risk ratio of 3.8. Similar results were noted in Finland [35]. Another study concluded that up to 42% of prostate cancer risk could be attributable to inheritable factors [36]. The absolute risk of prostate cancer for twins diagnosed up to the age of 75 was sixfold higher for mono- vs. di-zygotic twins (18% vs. 3%). It also showed a statistically significant shorter time interval between age at diagnosis times for monozygotic twins compared with dizygotic twins (5.7 yrs vs. 8.8 years; p=0.04).

**Segregation analyses**

Segregation analyses study the structure of familial clusters and describe the mode of inheritance, age-specific cumulative risk (penetrance), and allele frequency of genetic predisposition to a disease. Carter et al [30], using such analyses, suggested that prostate cancer diagnosed at <55 years may be due to a rare autosomal dominant highly penetrant allele which could account for up to 43% of disease in this age group and up to 9% of prostate cancer in men aged up to 85 years. Alleles for such a rare autosomal dominant gene were predicted to exist at a frequency of 0.003 and to cause a cumulative risk of disease of 88% by the age of 85 years compared with 5% for non-carriers. Other reports have reached similar conclusions, but with a commoner allele frequency and a lower penetrance of about 67% [Gronberg et al [32], allele frequency 0.0167; Schaid et al [37], allele frequency 0.006]. A recessive or X-linked model is suggested by some studies which noted higher risks to brothers of prostate cancer cases compared with fathers [38, 39]. Ewis et al (2002) [40] report an odds ratio of 2.04 (p=0.02) for allele C of dYs19 in Japanese prostate cancer patients, whilst other alleles of this region were protective (allele D, OR 0.26 p=0.002). The Y chromosome (father to son transmission) is therefore also implicated. It is possible that a mixture of several models exist giving rise to age-related risks [41]. Dominantly inherited risk allele(s) may explain early onset disease and a recessive or X-linked model could account for its later onset [42].

**Molecular analysis evidence**

**– linkage studies [genome wide scans]**

Linkage analysis involves a gene-hunting technique that looks for co-segregation of a disease in large, high-risk families, with disease-causing genetic mutations. Linkage analysis has been used to map many familial cancer loci e.g. colorectal cancer, breast/ovarian cancer, and melanoma reviewed in Eeles et al, 1996 [43]. Initially, linkage analysis narrows down the region within which a disease-causing locus may lie by analysing co-inheritance of polymorphic stretches of DNA such as microsatellite markers. The sequencing of the human genome will also make the use of single nucleotide polymorphisms (SNPs) possible and as these are more numerous than polymorphic runs of DNA sequence. These will enable denser linkage maps to be determined. Once a region of linkage is identified then candidate gene mutation analysis within the region is undertaken to identify the disease-causing mutation.

**Candidate gene analysis evidence**

**– BRCA2, NBS and CHEK2 genes**

The search for genetic markers of disease susceptibility often utilizes the candidate gene approach, where a gene is targeted based on the properties and metabolic pathways of its protein product. In the early nineties, prostate cancer cases were noted to be clustered within breast cancer families [44, 45]. The RR of prostate cancer in male carriers of mutations in the breast cancer predisposition genes BRCA1 and BRCA2 is increased. The RR with respect to BRCA1 was found to be 3.33 [46] and 1.82 in a further analysis by the BCLC [47]. That of BRCA2 was found to be 4.65. The RR is higher in men with prostate cancer diagnosed before 65 years (RR 7.33), with an estimated cumulative incidence by the age of 70 of 7.5-33.0%. A founder mutation 999del5 in BRCA2 has been identified in Iceland. This mutation is reported to confer a cumulative prostate cancer risk to carriers of 7.6% by the age of 70 [48]. Sixty seven percent of men who had the mutation all developed advanced prostate cancer and a high mortality [49], raising the possibility that BRCA2 predisposes to more aggressive disease. A report in a Swedish family carrying the BRCA2 mutation 6051delA [50] adds weight to the evidence that such mutations are pathogenic. A mutation screen of BRCA1 and BRCA2 genes was conducted by Gayther et al [51] in a set of 38 UK families. Two germline deleterious BRCA2 mutations were observed. A further study was conducted by Edwards et al [52] on 263 men aged <55 at diagnosis. The six pathogenic mutations found were interestingly outside the ovarian cancer cluster region in the gene, implying a genotype/phenotype correlation and accounted for 2% of prostate cancer at this young age. This equated to an RR of 23 by the age of 60 and conferred an absolute risk of prostate cancer
by the age of 55 of 1.3% and 10% by the age of 65. This supports the claim that BRCA2 is a high-risk prostate cancer gene. Two recent studies have reported an increased risk of prostate cancer associated with the Ashkenazi founder mutations in the BRCA genes, lending further evidence to these data [53, 54].

Subsequent to these reports, germline mutations have been found in the NBS gene in the Slavic population at a higher frequency in prostate cancer cases than controls [55] and in the CHEK2 gene [56]. This raises the possibility that prostate cancer predisposition may in some cases be due to mutations in genes in the DNA repair pathway that in the homozygous form give rise to a severe phenotype (in the case of BRCA2 this would be Fanconi’s anaemia D2 and in the case of NBS would be Nijmegen Breakage Syndrome), but in the heterozygous form, would give a risk of prostate cancer.

**Genome searches in prostate cancer**

The process of running a large number of microsatellites – typically in the region of 400, has many terms: Genome wide Scan, Genome wide Search or Genome wide Screen – and can conveniently be abbreviated to GWS. Numerous linkage analysis experiments have been undertaken across the genome to identify prostate cancer susceptibility loci. The ACTANE (Anglo-Canadian-Texan-Australian-Norwegian-EU Biomed) group has used a definition of age at onset and number of cases, but has also concentrated on the collection of clinically significant disease. This is because the disease manifests 10 years later on average than clinically detected disease and therefore men with early onset clinically detected disease would have had a raised PSA level at even earlier age and may therefore be enriched for genetic predisposition [28].

Thus far, several GWS have been reported for prostate cancer. [1, 3, 5, 57-72]. The significant results are summarised as follows:

**1q23-24: HPC1 and the RNASEL data.** The first GWS identified a locus named HPC1 (Hereditary Prostate Cancer 1) at 1q24-25. A group from Johns Hopkins University, Baltimore, conducted the study in 91 North American and Swedish families and their report suggested that 34% of families may be linked to this locus [1]. Various groups have since have either confirmed [73-76], or refuted [57, 58, 60, 64, 77, 78] the original observation. Goode et al [64], and Goddard et al [79] found evidence of linkage in families with more aggressive prostate cancer.

A meta analysis conducted by Xu et al [80] representing many groups, comprising the International Consortium for Prostate Cancer Genetics (ICPCG), reported data obtained on 772 families and found that a lower estimate of 6% of all families were linked to 1q24-25. A more refined analysis concluded that HPC1 may play a role in a subset of families with numerous young onset cases, particularly among black men. Carpten et al [81] subsequently found mutations in the cell proliferation and apoptosis regulating gene RNASEL which was in this region. Of 8 families that were linked to the 1q region, two had germline mutations, one was a stop Glu265Ter (E265X) termination codon but the other was a missense mutation. Neither segregated with the disease. Some, but not all further reports have shown RNASEL mutations to be associated with prostate cancer, but with a much lower relative risk than would be predicted by the linkage evidence. Rokman et al [82] showed that the Glu265X in RNASEL was present 4.5-fold more often in affected family members compared with controls. Other groups have found that RNASEL may confer much smaller prostate cancer risks or have found no mutations at all in prostate cancer cases, therefore it is not a highly penetrant prostate cancer gene which is in conflict with the linkage evidence [83, 84]. This suggests that the linkage results are misleading or that a highly penetrant HPC1 exists but is still to be found.

**Other loci and candidates from GWS.** Other loci follow a similar pattern as described above i.e. loci are identified that have significant LOD scores and candidate genes have mutations described therein which are then refuted, or whose risks fall on further detailed scrutiny [85, 86].

**Other significant loci:**

**PCaP (1q42.2-43; Berthon et al [57])** – this was a locus identified in the German/French population, but not confirmed by other groups. **CAPB (1p36; Gibbs et al. [59])** – a locus associated with primary brain tumour and prostate cancer which on further analysis was probably more associated with young onset prostate cancer rather than brain tumour [87]. A locus has been described on chromosome 16q in sibling pairs by Suarez et al [58], and one on 20q (**HPC20**) by Berry et al [63]. These are still to be confirmed. A further locus has been described on the long arm of chromosome X (**HPCX; Xq27-28**) by Xu et al [88]). This has been confirmed by some other groups, but the gene has not yet been identified. There are also loci that have been found to be associated with more aggressive disease e.g. 7q, 19q [89-91]. Eight GWS have been published recently in one issue of the Prostate (ACTANE Consortium [72]; Lange et al [65]; Schleutker et al [66]; Cunningham et al [67]; Xu et al [68]; Wiklund et al [80]).
A summary of these was published in an accompanying review by Easton (2003) [5]. The conclusion of these GWS to date is that there are numerous loci suggested by the GWS from various groups which are not consistently replicated by independent groups on study of further prostate cancer families. This implies that there is considerable genetic heterogeneity.

Low penetrance genes. The possibility that a disease is due to a combination of low penetrance, more common genetic variants may be entertained when large families are rare and it is difficult to locate predisposition genes by linkage. Candidate studies of polymorphisms are presently underway in prostate cancer and there is currently no uniform pattern of polymorphisms which confers increased risk from the data. However, the most consistent polymorphisms to date that confer a moderately increased risk are in the SRD5A2, GSTP1 and the AR genes, [92-102].

Optimising prostate cancer predisposition gene discovery in the near future – issues to be addressed

The are several uncertainties in the area of genetic predisposition which are currently taxing researchers in this area. These include (a) what is the optimal genetic model? (b) are there different predisposition genes in different populations? and (c) how much agreement is there between various groups for the putative loci? The results of future large scale multicentre studies will potentially answer these questions.

Combining data. It is possible that the studies undertaken thus far are underpowered, and pooling of data may improve the chances of finding the true underlying linkage. This is the aim of the creation of groups such as ICPCG. Groups undertaking linkage analyses worldwide collaborate within this consortium. In 2000, via a meta-analysis, this group found that the 1q24 locus may contribute to about 6% of prostate cancer families and was more common in larger prostate cancer clusters whose average age of onset was <65 years [80].

Clinical vs. Screen Detected Disease. Current data suggest that progression to clinical disease is more likely following a raised PSA and occurs a median time of 10 years after the PSA has risen [103]. In theory, patients in families that are diagnosed with clinically detected disease may have different genes to those involved in PSA screen detected patients. At present, whether this is true, this is unknown.

Genetic heterogeneity for linkage: more than one prostate cancer predisposition gene. The fact that 2% of early onset cases have deleterious mutations in the BRCA2 gene and that a further small percentage is due to NBS and CHEK2 mutations and yet models suggest that up to 43% of such cases may harbour a predisposition gene [30], indicates that there are further prostate cancer susceptibility genes to be discovered.

Many instead of one prostate cancer predisposition gene per family. In an age when the majority of monogenic human disease genes have been identified, a particular challenge for the coming generation of human geneticists will be resolving complex polygenic and multifactorial diseases. It is likely that the majority of genetic predisposition to prostate cancer will follow this model.

Current clinical management concepts in hereditary prostate cancer

The question of whether a genetic change influencing prostate cancer causation is associated with factors altering treatment response needs to be addressed. Recent reports are conflicting. Carefully documented multi-institutional, prospective family history data collection and outcome analysis are vital to optimising our understanding of this condition. The current management issues surrounding hereditary prostate cancer (HPC) involve several components: (i) the degree of biological aggressiveness of HPC, (ii) whether HPC is an independent predictor of treatment outcome, (iii) whether there is a difference in the survival curves between sporadic and HPC and (iv) the outcome patterns in those patients treated with radical prostatectomy vs. radiotherapy by family history.

Determining the degree of biological aggressiveness

Walsh initially observed that there was no significant difference between phenotypes of sporadic, familial and HPC undergoing radical prostatectomy with respect to clinical stage, pre-op PSA, PSA density, prostate weight, Gleason score, pathologic stage or tumour histology [104]. This was later challenged by the observation that patients with localized prostate cancer who reported a positive family history may have a worse outcome at three and five years following either radiation therapy or surgery than those with sporadic cancers [105]. This was then again refuted by three further studies which found no difference in the aggressiveness of HPC versus sporadic disease [106-108]. This area therefore remains controversial.
Is HPC an independent predictor of treatment outcome?

Kupelian et al [108] first demonstrated that the presence of a family history of prostate cancer correlates with treatment outcome in a large unselected series of patients and suggested that familial prostate cancer may have a more aggressive course than nonfamilial prostate cancer. Further studies are currently underway to validate this finding.

Survival differences between sporadic and HPC

No significant differences in either overall or cause-specific survival were found between sporadic, familial, and HPC patients [109]. At present it seems plausible that treatment plans should not differ based on presence or absence of familial prostate cancer, but further work is needed to substantiate this.

Should men with a family history of prostate cancer be treated rather than observed?

Based on the current body of evidence there seems to be a rationale for genetic screening of men at risk once genes responsible for prostate cancer are identified. The American Urological Association recommends that men who are at high risk for developing prostate cancer such as men with a family history of the disease, or men of African-American descent begin receiving routine prostate cancer screening at the age of 40 [110]. The American Cancer Society recommends that men receive PSA or digital rectal examination testing annually at the age of 50, or earlier if they have a family history of the disease or are of African-American descent [111].

Outcome patterns in HPC men treated with radiotherapy vs. radical prostatectomy

Hanlon et al [112] found no difference in biochemical failure rates between carefully matched men with and without a family history of prostate cancer. This supports other studies that failed to show an increased risk of failure after definitive therapy for clinically localized prostate cancer in men with either combined hereditary and familial and patients with the sporadic form of prostate cancer.

Chemoprevention trials

Prostate cancer chemoprevention is the administration of agents that inhibit one or more steps in prostatic carcinogenesis. The main components of chemoprevention include agents and their molecular targets, strategic intermediate endpoint biomarkers and their critical pathways and cohorts identified by genetic and acquired risk factors [113]. The identification of genetic susceptibility loci would enable a group of men at high risk of developing prostate cancer to be identified to serve as subjects for chemoprevention trials. If such trials yield positive results, they potentially could lead to a recommendation for preventative therapy in genetic mutation carriers. Several putative chemopreventive agents are currently being investigated. Results of a population-based, randomized phase III trial demonstrates that finasteride may prevent prostate cancer. However, the paper suggested that only low grade tumours were prevented and in fact the number of high grade tumours was greater in the finasteride arm. Clarke et al [114] studied the impact of supplemental dietary selenium on the change in the incidence of prostate cancer. They found that although selenium shows no protective effects against the primary study endpoint of squamous and basal cell carcinomas of the skin, the selenium-treated group in their series had substantial reductions in the incidence of prostate cancer as a secondary endpoint. Further studies are clearly indicated. Preliminary data seem to suggest at least some benefit with the use of other agents as potential preventatives in addition to selenium. These include vitamin E, vitamin D, other 5-alpha-reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene, and green tea. Some of these agents are being tested in new large-scale phase III clinical trials [115]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), is an intergroup phase III clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer and aims to build on secondary analyses of large-scale chemoprevention trials [116]. The emergence of new powerful tools such as proteomic analysis of tissue based and secreted proteins [117] and gene chip cDNA microarrays for multiplex gene expression profiling would optimise the identification of new molecular targets, cohorts at risk and the design of suitable combination trials.

Targeted screening

Several controversies surround the management of relatives of prostate cancer patients. Targeted screening studies have shown a higher percentage of raised PSA levels in relatives of cases in families compared with sporadic cases. In a screening study of prostate cancer in high-risk families done by McWhorter et al [118] it was shown that previously unsuspected and clinically relevant cancers were found in 24% of a total of 34 first-degree
relatives, compared to the approximately 1 (3%) expected
($p<0.01$). The study emphasized the importance of
thorough screening in first-degree relatives of prostate
cancer patients. The first targeted screening study based
on BRCA1/2 genotype will start later this year (the
IMPACT study; Tischkowitz and Eeles, 2003) [119].
Targeted screening can be achieved by monitoring serum
PSA levels in relatives of young or early onset prostate
cancer or families with multiple cases. Counselling about
the uncertainties of optimal age at which screening
should be initiated is of paramount importance. The
sub-thirty and sub-forty year old groups would not be
screened by most authorities. Most would start screening
either at age five years younger than youngest age at
diagnosis of a relative or forty years, but not normally
younger than this.

Proteomics and bioinformatics

With the recent exponential increase in the development and
improvement of techniques involving proteomics, there has been a dramatic increase in the
likelihood of finding clinically relevant candidate genes,
gene clusters and signalling pathways. This would
potentially extrapolate itself into better diagnostic and/or
more specific targeted therapeutic plans in the
management of sufferers of prostate cancer [119, 120].

Summary

Prostate cancer inheritance following a simple
Mendelian pattern may be identified in the families of
proband with early-onset cases. At present, the only
clinically applicable measure to try to reduce prostate
cancer mortality in families with hereditary disease is
screening, which aims to diagnose the disease when it
is still in a curable stage. The specific mechanism of how
gene mutations contribute to an increased susceptibility
for prostate cancer remains elusive but the finding of
germline mutations in the BRCA2, CHEK2 and NBS1
genes suggest that at least a proportion may occur due
to mutations in the DNA repair pathway. This would have
implications for treatment of such individuals with DNA
damaging agents. It is likely that the cause of the majority
of prostate cancer cases will be multifactorial and will
involve genetic and environmental factors.

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