

Familial Prostate Cancer

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Prostate cancer (PCa) is the most common cancer diagnosed in North American men, excluding skin cancers. It is estimated that, in 2004, approximately 230,110 new cases and 29,900 prostate cancer-related deaths will occur in the United States [1]. In Australia, one in 11 men will develop the disease during their lifetime [2]. The annual number of new cases registered in England and Wales increased by over threefold between 1971 and 2004, from 6174 to over 21,000 [3] (www.icr.ac.uk/Everyman). Prostate cancer remains a major public health problem.

Several risk factors for the disease have been suggested, including diet, sexually transmitted agents, and endocrine factors [4]. However, none of these environmental factors has been confirmed to have a significant causative effect on PCa. Current known risk factors include race [5,6] and a positive family history of the disease. The degree to which the differences in these cohorts can be attributable to environmental factors is unclear.

Over the last 45 years, prostate cancer has been observed to run in families. Familial aggregation (at least two cases in the family) has been observed in around 20% of cases and a hereditary form of PCa in approximately 5% [7]. Epidemiological evidence shows familial clustering of PCa, and it is currently established that a positive family history is a strong risk factor.

One of the major issues surrounding familial prostate cancer (FPC) includes identifying gene(s) predisposing to PCa in families at high

risk. If a predisposition gene(s) could be characterized, then those at increased risk of PCa can be potentially identified and offered modes of prevention and targeted screening. The other major issue is the clinical management of patients who are known to have a family history of prostate cancer.

Evidence for the Genetic Etiology of Prostate Cancer

Evidence for familial aggregation of prostate cancer dates as far back as 1956 [8]. Significant linkage in familial prostate cancer was first published in 1996 by a group from Johns Hopkins University, Baltimore, Maryland [9]. This group reported linkage at a locus on chromosome 1q24-25, which was named hereditary prostate cancer 1 (*HPC1*). Several large linkage studies have since been conducted, and the results revealed new loci and challenged others [summarized in refs. 10–13].

So far, genotyping data have been reported in over 1600 families. There are numerous conflicting reports supporting or refuting linkage within many areas in the genome. This challenges our understanding of the genetic basis of this disease. This search is distinct from the search for a familial breast cancer predisposition gene, in which analysis of linkage in select regions revealed a site where the *BRCA1* gene was situated [14]. This work shows that the

genetic predisposition to PCa is highly complex, probably involving numerous predisposition genes, and that a high proportion of high-risk families may not be due to a single high-risk gene.

Epidemiological Evidence

It was observed in the 1950s and 1960s that the risk of PCa in relatives of sufferers was higher [15,16]. Early observations were made in large families in Utah [17,18] in which PCa seemed to cluster. To appreciate the evidence of a familial component, case control, cohort and twin studies, must be explored.

Case-Control Studies

Case-control studies can be grouped into two main types. The first type compares PCa incidence in first-degree relatives of affected

patients (cases) with the incidence in the relatives of cancer free men (controls). The second type compares the fraction of PCa cases vs. controls with a positive family history of the disease [15–17,19–34]. These studies are summarized in Table 2.1.

These studies indicate that the relative risks (RR) in first-degree relatives of PCa patients range from 0.64 to 11.00-fold [summarized in refs. 35–37]. With the single exception of the RR of 0.64 [19], in a study that was done on a small sample set of 39 families, 15 of these 16 studies reported an RR of 1.76 or higher. Furthermore, the RR has been observed to increase when more than one relative is affected. Steinberg et al. [23] in 1990 showed that the RR with an affected first-degree relative was 2.0 and with a second-degree relative was 1.7, but with both first- and second-degree relatives combined the RR rose considerably, to 8.8. It was also observed that the RR increased as the number of family members increased, with RRs of 2.2, 4.9, and 10.9 for one,

Table 2.1. A comparison of case-control studies

Reference	No. of cases	No. of cases in first-degree relatives of:		Relative risk
		Cases	Controls	
Morganti et al., 1959* [8]	183	11	1	11.0
Woolf, 1960† [16]	228	15	5	3.0
Krain, 1974* [20]	221	12	2	6.0
Fincham et al., 1990* [24]	382	58	31	3.2
Cannon et al., 1982† [17]	2824	‡	‡	2.4
Meikle et al., 1985† [22]	150	11	1	4.0
		Brothers only		(at age 80) 16.6
Isaacs et al., 1995* [29]	690	119	55	(at age <49) 1.76
Keetch et al., 1995† [30]	1084	273§	85	3.40
% with positive family history		%	%	
Steele et al., 1971* [19]	39	12.8	20.0	0.64
Schuman et al., 1977* [21]	40	16.7	7.3	2.30
Steinberg et al., 1990* [23]	691	15.0	8.0	1.90
Spitz et al., 1991* [25]	378	13.0	5.7	2.30
Ghadirian et al., 1991* [26]	140	15.0	2.0	7.50
Ghadirian et al., 1997† [32]	640	15.0	5.0	3.32

* Information from patient/control questionnaire only.

† Diagnosis verified by hospital records, cancer registration or death certificate.

‡ Measured genealogical index; see Neuhausen, et al. (Br J Urol 1997;79).

§ First- and second-degree relatives.

Table 2.2. Relative odds for prostate cancer in brothers of prostate cancer cases by age

Age of affected case	Age of brother (years)		80+
	<65	65–79	
<65	5.97**	2.77*	2.29
65–79	2.77*	2.04**	2.52*
80+	2.29	2.52*	1.14

* $p < .01$; ** $p < .001$.

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two, and three additional affected relatives besides the proband, respectively. This is strong evidence for at least a genetic *component* in pre-disposition to familial disease. The observed increases in RR are too large to be explained by an environmental effect alone.

Another interesting observation is that the RR to family members increases as the age of the proband decreases [17,38], rendering further support to a genetic role. This pattern, in which the relative risk markedly increases as the age of the proband decreases, offers some of the best evidence that there is a genetic role (Table 2.2). This table is helpful in risk assessment for genetic counseling. A brother of a proband with prostate cancer at age 50 has a 1.9-fold higher risk of developing prostate cancer compared with a brother of a man diagnosed with the disease at age 70 [38]. As the closeness and number of affected members in the family increases (Tables 2.3 and 2.4), and when both factors are taken together, there is a marked increase in the level of RR (Table 2.5).

Table 2.3. Relative risks for prostate cancer in relatives of prostate cancer cases by degree of relationship

Affected relatives	Relative risk (95% confidence interval [CI])
First-degree	2.0 (1.2–3.3)
Second-degree	1.7 (1.0–2.9)
Both first- and second-degree	8.8 (2.8–28.1)

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Table 2.4. Age-adjusted relative risk estimates for prostate cancer by number of additional affected family members

Affected relatives (besides proband)	Odds ratio (95% CI)
1	2.2 (1.4–3.5)
2	4.9 (2.0–12.3)
3	10.9 (2.7–43.1)

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Cohort Studies

One of the potential pitfalls in the studies conducted is the potential bias introduced by focusing on an unselected population. Cohort studies attempt to avoid this bias. Goldgar et al. [39] showed a familial PCa RR of 2.21 in first-degree relatives of 6350 probands from an unselected PCa population from the Utah Population Database. In another study involving 5496 sons of Swedish men from Cancer Registry data, Gronberg et al. [40] found a RR of 1.70.

Twin Studies

Several twin studies show an increased RR in mono- compared with dizygotic twins of just over three- to sixfold [41]. In a study by Page et al. [42] on 15,924 male twin pairs, they found that pair-wise concordance (twins where both men had PCa) rates among monozygotic twins was 15.7%, while that of dizygotic twins was 3.7% ($p = < .001$). Proband-wise concordance (number of concordant affected twins divided by total number of affected twins) was 27.1%

Table 2.5. Estimated risk ratios for prostate cancer in first-degree relatives of probands, by age at onset in proband and additional family members

Age at onset of proband	No. of additional relatives affected	One or more additional first-degree relatives affected
50	1.9 (1.2–2.8)	7.1 (3.7–13.6)
60	1.4 (1.1–1.7)	5.2 (3.1–8.7)
70	1.0*	3.8 (2.4–6.0)

* Reference group.

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA. 1992 Apr 15;89(8):3367–3371.

for monozygotic twins and 7.1% for dizygotic twins, which gives a risk ratio of 3.8. These results were supported by another study in Finland [43]. Lichtenstein et al. [44] showed in another study that up to 42% of PCa risk could be attributable to heritable factors. The absolute risk of PCa for twins diagnosed up to age 75 was sixfold higher for mono- versus dizygotic twins (18% vs. 3%). The time interval between age at diagnosis for monozygotic twins compared with that for dizygotic twins (5.7 years vs. 8.8 years; $p = 0.04$) was shorter, and this was statistically significant. These data all support a genetic component for PCa, possibly from multiple interacting genes.

Segregation Analyses

Despite the fact that the case-control studies described support the significance of genetic factors in the development of PCa, the genetic mode of transmission is still debated. 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. [38], using such analyses, observed that PCa diagnosed at < 55 years might be caused by 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 PCa in men aged up to 85 years. Alleles were predicted to exist at a frequency of 0.003 and to cause a cumulative risk of PCa of 88% by age 85 years versus 5% for noncarriers. Similar conclusions have been reached by other reports, but with a higher allele frequency and lower penetrance of about 67% (Gronberg et al. [40], allele frequency 0.0167; Schaid et al. [45], allele frequency 0.006). Some studies noted higher risks to brothers of prostate cancer cases compared with fathers [46,47], suggesting a recessive or X-linked model. Ewis et al. [48] reported an odds ratio of 2.04 ($p = .02$) for allele C of dYs19 in Japanese PCa patients, whereas other alleles of this region were protective [allele D, odds ratio (OR) 0.26, $p = .002$]. Thus the Y chromosome (father to son transmission) also seems to be implicated. It is possible that several models coexist, giving rise to the observed age-linked risks [49]. Dominantly inherited risk allele(s) could partially explain early-onset PCa, and a

recessive or X-linked model could account for its later onset [50].

Molecular Analysis Evidence: Linkage Studies

In contrast to other common cancers such as breast and colon cancer, in which a small number of high-risk genes account for a percentage of the high-risk multiple case families, familial PCa is likely to be caused by numerous different genes. Linkage analysis is performed by using a gene-hunting technique that identifies co-segregation of the disease in large, high-risk families, with disease-causing genetic mutations. Linkage analysis has been used to map many familial cancer loci, for example, colorectal cancer, breast/ovarian cancer, and melanoma [reviewed in ref. 51]. By analyzing co-inheritance of polymorphic stretches of DNA, linkage analysis focuses on the region within which a disease-causing locus may lie. Having identified a region of linkage, 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 candidate gene approach is used to search for genetic markers of disease susceptibility, where a gene is targeted based on the characteristics of its protein product. PCa cases were noted, in the early 1990s, to be clustered within breast cancer families [52,53]. The RR of PCa 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 [54] and 1.82 in a further study by the Breast Cancer Linkage Consortium (BCLC) [55].

For *BRCA2*, the RR was found to be 4.65 in the BCLC series. The RR is higher in men with PCa diagnosed before 65 years (RR 7.33), with an estimated cumulative incidence by age 70 of 7.5% to 33.0%.

A founder mutation in *BRCA2* mutation is reported to confer a cumulative PCa risk to carriers of 7.6% by age 70 [56]; 67% of men who had the mutation developed advanced PCa with a high mortality [57]. This raised the possibility that *BRCA2* predisposes to more aggressive disease. A report in a Swedish family carrying a deleterious *BRCA2* mutation [58] supports the evidence that such mutations could be pathogenic. Gayther et al. [59], in a set of 38 United Kingdom families, conducted a mutation screen of *BRCA1* and *BRCA2* genes. Two germline deleterious *BRCA2* mutations were observed. A further study was conducted by Edwards et al. [60] on 263 men aged ≤ 55 at diagnosis, and they found six pathogenic mutations. Interestingly, these were downstream of the ovarian cancer cluster region, which is central in the gene, implying a genotype/phenotype correlation. The mutations accounted for 2% of PCa diagnosed at this young age. This equated to a RR of 23-fold by 60 years of age and an absolute risk of PCa of 1.3% by age 55 and 10% by age 65. This seems to support claims that *BRCA2* is a high-risk PCa gene. More recently, studies reported an increased risk of PCa in conjunction with the Ashkenazi founder mutations in the *BRCA1* and *BRCA2* genes [61,62].

Following these initial observations, germline mutations have been found in the *NBS* gene at a higher frequency in PCa cases than controls [63], albeit only in a founder Slavic population to date, and in the *CHEK2* gene [64]. This raises the possibility that PCa predisposition in a proportion of cases might be caused by mutations in the DNA repair pathway genes. It is thought that these gene mutations in the homozygous form may give rise to a severe phenotype (in the case of *NBS* this would be the Nijmegen breakage syndrome and in the case of *BRCA2* this would be Fanconi anemia D2). However, in the heterozygous form, there would be a risk of getting PCa.

Genome Searches in Prostate Cancer

A genome-wide search (GWS) involves the process of running a large (typically in the region of 400) number of microsatellite markers throughout the genome to locate disease-

predisposing genes by looking for cosegregation of markers with the disease in families. The attempt to identify prostate cancer susceptibility loci has been undertaken across the genome by numerous groups. The Anglo-Canadian-Texan-Australian-Norwegian-European Union Biomed (ACTANE) group has defined age at onset and number of cases and focused on the collection of clinically significant PCa, because the disease manifests 10 years later on average than prostate-specific antigen (PSA)-detected disease, and hence men with clinically detected early-onset PCa could have had a raised PSA level at an earlier age [36].

Thus far, several GWSs have been reported for prostate cancer [9,11,13,65–80]. The significant results are summarized as follows:

1q23-24: *HPC1* and the *RNASEL* Data

A group from Johns Hopkins University, Baltimore, Maryland, conducted a study in 91 North American and Swedish families, and its report suggested that 34% of families might be linked to this locus [9]. This GWS identified a locus named *HPC1* (hereditary prostate cancer 1) at 1q24-25. Various groups have since either confirmed [81–84], or challenged [65,66, 68,72,85,86] the Hopkins' observation. Goode et al. [72], and Goddard et al. [87] identified evidence of linkage in families with more aggressive PCa.

Xu [88], in a meta-analysis, found that approximately 6% of all PCa families were linked to 1q24–25. A further analysis concluded that *HPC1* might play a role in a subset of families with several young-onset cases especially in African-American men. Carpten et al. [89] subsequently found mutations in the cell proliferation and apoptosis regulating gene *RNASEL*. Some reports have shown *RNASEL* mutations to be associated with PCa, but with a much lower RR than would be extrapolated by the linkage evidence. Rokman et al. [90] showed that the Glu265X in *RNASEL* was present 4.5-fold more often in affected family members compared with controls. *RNASEL* was found by other groups to confer much smaller PCa risks or have found no mutations in this gene in PCa families. *RNASEL* seems not to be a highly penetrant prostate cancer gene, which seems to conflict with current linkage evidence [91,92].

Other Loci and Candidates from GWS

Other loci have been identified that have significant logarithm of odds (LOD) scores or whose risks fall on further detailed scrutiny [93,94].

Other Significant Loci

PCaP (1q42.2–43 [65]) was a locus identified in the German/French population, but not confirmed by other groups. *CAPB* (1p36 [67]) is a locus associated with primary brain tumor and PCa, which on further analysis was probably more associated with young-onset PCa rather than brain tumor [95]. Suarez et al. [66] described a locus on chromosome 16q in sibling pairs. Berry et al. [71] described another one on 20q (*HPC20*). These are still to be confirmed. It is likely that the *HPC20* locus is not real, as recent analyses from multiple groups in the International Consortium for Prostate Cancer Genetics (ICPCG) have failed to confirm linkage to this locus in a meta-analysis (Schaid and the ICPCG, in press, 2004). A further locus has been described on the long arm of chromosome X (*HPCX*; Xq27–28) by Xu et al. [96]. Some loci, for example, 7q, 19q [97–99], have been found to be associated with more aggressive PCa. Eight GWSs have been published recently in one issue of *The Prostate* (ACTANE Consortium [80]; Lange et al. [73]; Schleutker et al. [74]; Cunningham et al. [75]. Xu et al. [76]; Wiklund et al. [77]; Janer et al. [78]; Witte et al. [79]). This work was summarized in an accompanying review by Easton et al. [13]. The conclusion of these GWSs to date is that there is considerable genetic heterogeneity.

Low-Penetrance Genes

Some of the genetically acquired risks of inheritance of PCa could be due to common low-penetrance genes. A significant association between a susceptibility to PCa and common genetic variants, for example, the androgen receptor (AR) genes, has been observed. Although the AR has been excluded as a site for a highly penetrant dominant PCa susceptibility locus, it is a candidate for a lower penetrance PCa susceptibility gene. The most consistent polymorphisms to date that confer a moderately

increased risk are in the *SRD5A2*, *GSTP1* and *AR* genes [100–110].

Clinical Management

About 10% of PCa cases are thought to be due primarily to *high-risk* inherited genetic factors or PCa susceptibility genes. Men with a father or brother with PCa are twice as likely to develop PCa as men with no affected relatives. The risk increases with increasing number of relatives that are affected, for example, men with two or three first-degree relatives affected have a fivefold and 11-fold increased risk of PCa, respectively (see Tables 2.1 to 2.5).

With the increase in PCa awareness among patients and health care professionals, an increasing number of people are querying the optimal management of individuals with a family history of PCa. The clinical management of FPC remains a challenge. Due to the significant number of men with a family history of PCa, the appreciation and understanding of key management issues is critical.

The current clinical management issues surrounding FPC involves several components: (1) biological aggressiveness, (2) outcomes following definitive treatment, (3) survival curve differences between FPC and sporadic cases, (4) treatment vs. observation in screen-detected patients, (5) role of chemoprevention, (6) role of targeted screening, and (7) genetic counseling.

Biological Aggressiveness

The biologic aggressiveness of FPC has been the focus of interest of several investigators. Walsh [111] first noted that there was no significant difference between phenotypes of hereditary, familial, and sporadic prostate cancer among those who underwent radical prostatectomy with respect to preoperative PSA, PSA density, Gleason score, tumor histology, pathological stage, or clinical stage. Kupelian et al. [112] later observed that men with localized PCa with a positive family history may have a worse outcome at 3 and 5 years following either radiation therapy or surgery than those with sporadic cases. Three further studies found no difference in the aggressiveness of the disease in familial compared with sporadic cases [113–115].

These seemingly equivocal results can partially be explained by the heterogeneous nature of the various target groups studied, bias in the self-reporting of family history, and the different subgroups of family history, for example, single first-degree versus multiple relatives with PCa. Recently, *E2F3* expression was found to be a potential independent factor in predicting overall survival of patients with PCa [116]. Such prognostic markers, if replicated in FPC, would be useful in identifying a subset of FPC that has a poorer prognosis.

Outcomes Following Definitive Treatment in Familial Prostate Cancer

Kupelian et al. [117] conducted a study to determine if FPC patients have a less favorable prognosis than patients with sporadic PCa after treatment for localized disease with definitive treatment, that is, either radical prostatectomy or radiotherapy. The 5-year biochemical relapse-free survival rates for patients with negative and positive family histories were 52% and 29%, respectively ($p < .001$). This is the first study that demonstrated that the presence of a family history of PCa correlates with treatment outcome and suggests that FPC may have a more aggressive course than nonfamilial PCa. Further studies are currently underway to validate this finding.

In patients not stratified as having FPC, biochemical failure rates were shown to be similar irrespective of whether radical prostatectomy or radiotherapy was the monotherapy undertaken for clinically localized PCa [118]. Eight-year biochemical failure rates were found to be identical in men treated with either radical prostatectomy or radiotherapy [119]. With respect to FPC, the key question is whether the outcomes are different between those offered different modes of monotherapy. Hanlon and Hanks [120], in an attempt to evaluate biochemical outcome after definitive radiotherapy as a function of family history groupings, found no significant difference in biochemical failure rates between carefully matched men with and without FPC. The findings of this study support others that failed to show an increased risk of failure after definitive therapy for clinically localized PCa in men with familial disease.

Azzouzi et al. [121] compared the biological and clinical features of sporadic and familial clinically localized PCa treated with radical prostatectomy, and found that the outcome is similar in those with and without a family history.

Large-scale prospective family history data collection and outcome analyses, therefore, need to be done to see whether a genetic change influencing PCa etiology correlates with factors altering treatment response.

At present the comparative roles of radiotherapy versus radical prostatectomy in the management of men with FPC are not ratified by robust studies; however, preliminary studies seem to suggest that outcome in FPC is not influenced by the mode of definitive therapy.

Sporadic and Familial Prostate Cancer: Biochemical Failure and Differences in Survival

Gronberg et al. [122] tried to estimate the survival of men with FPC and compare them with prostate cancer cases unselected for family history. No significant differences in either overall or prostate cancer-specific survival between familial and sporadic cases were found.

Tumor grade at diagnosis in familial cases did not differ from that in a population with prostate cancer unselected for family history. The conclusion, based on the result from this study, was that no differences in treatment between men with and without a positive family history of prostate cancer are justified.

However, Kupelian et al. [123], in an analysis of the outcome after radical prostatectomy of patients with familial versus sporadic prostate cancer, observed that the former group has a higher likelihood of biochemical failure after radical prostatectomy. They concluded that this effect was independent of pretreatment or pathological factors. Currently, it may be reasonable to recommend that treatment plans should not be altered based on presence or absence of FPC, but further large-scale studies are needed.

Treatment Versus Observation in Screen-Detected Patients

If highly penetrant genes responsible for PCa, such as the results of risk due to germline muta-

tions in *BRCA2*, were replicated, there would be a rationale for offering genetic counseling and testing for this disease. At present, these results should be replicated on a further sample set of blood samples from PCa cases diagnosed at young age prior to offering clinical diagnostic *BRCA2* genetic counseling and testing, and this is in progress in the U.K. Familial Prostate Cancer Study [10].

The American Urological Association currently recommends that men at high risk of developing PCa, that is, those with a family history of the disease or men of African-American descent, begin receiving routine prostate cancer screening at age 40 [124]. Its recommendation is that such men receive PSA testing and digital rectal examination (DRE) annually starting at age 50. This is recommended earlier if there is a family history of the disease or if one is of African-American descent, as above [125].

However, the exact age for initiation of screening has yet to be clearly defined. A targeted screening study using PSA alone in first-degree relatives of men diagnosed at <65 years or relative pairs with an average age of onset of 70 years or three or more relatives diagnosed at any age is underway in South Thames (the Cancer Research U.K. TAPS study, principal investigator Dr. Melia). The age of screening in different ethnic groups is currently under debate and further adds to the complexity of defining an optimal age for screening. Those men, however, found to be positive for PCa following the screen should be treated as documented in current clinical guidelines irrespective of family history.

The main recent area of controversy is the utility of the PSA value, particularly at low levels (see below) [126]. In the finasteride chemoprevention study, all men were offered biopsy, and 15% of those with a PSA of <1.5 had histological prostate cancer. The dilemma is that these diagnoses may not be clinically significant, and better progression markers are needed both in sporadic and familial disease.

Role of Chemoprevention

The chemoprevention of PCa involves the delivery of agents that could potentially inhibit the crucial carcinogenic steps in its development.

The characterization of genetic susceptibility loci could enable men at high risk of developing PCa to be identified and to serve as subjects for chemoprevention trials. Provided these trials yield positive results, they could potentially lead to a recommendation for preventative therapy in genetic carriers.

The key components of chemoprevention include specific agents and their biochemical targets, intermediate end-point biomarkers, with their critical pathways and cohorts identified by both genetic and acquired risk factors [127]. Several putative chemopreventive agents are currently under investigation. Results of a population-based, randomized phase III trial demonstrate that finasteride may prevent PCa. However, the study was slightly disappointing in that only low-grade tumors seem to have been prevented, and in fact the number of high-grade tumors was greater in the finasteride group [126].

Clarke et al. [128], in their study of the role of selenium, found that although selenium shows no protective effect against the primary end point of squamous and basal cell carcinomas of the skin, the selenium-treated group in their series had substantial reductions in the incidence of PCa as a secondary end point. Preliminary data seem to indicate that there may be some benefit with the use of other agents as potential preventatives in addition to selenium. These include vitamin E, vitamin D, other 5 α -reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene, and green tea. Some of these agents are being tested in new large-scale phase III clinical trials [129].

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a phase III clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer [130]. Refinements in new powerful tools such as proteomic analysis of tissue-based and secreted proteins [131] and gene chip complementary DNA (cDNA) microarrays for multiplex gene expression profiling could help optimize the identification of new molecular targets, cohorts at risk, and the design of suitable combination trials.

The patient with FPC may benefit from the use of chemopreventive agents, and the results of further large-scale trials will define its putative role in the future. The prospect of recommending surgical prophylactic therapy in

genetic mutation carriers would be extremely controversial.

Targeted Screening

Targeted screening studies have shown a greater proportion of raised PSA levels in relatives of patients as compared to sporadic cases of prostate cancer. In a screening study of prostate cancer in high-risk families performed by McWhorter et al. [132], 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 one expected ($p < .01$). This emphasizes the importance of PSA screening in first-degree relatives of prostate cancer patients. Targeted screening can be done by checking serum PSA levels in relatives of young- or early-onset PCa patients or families with multiple cases. It is reasonable to start screening either at age 40 or 5 years younger than the youngest age at diagnosis of a relative (whichever is the higher).

The first targeted screening study based on *BRCA1/2* genotype will start later this year (the Identification of Men with Genetic Predisposition to Prostate Cancer and Its Clinical Treatment [IMPACT] study [133]). Several large units have already started targeted screening programs with the objective of identifying markers of disease aggression. The programs have been initiated despite the established general setbacks of PSA screening, including lack of clearly defined optimal intervals between individual screens, increased false-negative biopsy rates, and diagnosis and subsequent management of incidentally found prostatic intraepithelial neoplasia.

Genetic Counseling and Testing/Research

Currently, genetic analysis (e.g., *BRCA2* mutation analysis) should be performed only within the context of a research study that will determine penetrance and genotype-phenotype correlation of specific mutations. The criteria for the Cancer Research U.K./British Prostate Group/British Association of Urological Surgeons' Section of Oncology Familial Prostate Cancer Study (principal investigator Dr. Eeles) are as follows:

- Men with PCa diagnosed at <60 years
- Affected relative pairs with PCa where one is <65 years at diagnosis
- PCa families with three or more members diagnosed at any age

Even in the absence of genetic testing, African-American men and men with a strong family history of prostate cancer (as defined in the TAPS study, see above), may opt to initiate screening by PSA and DRE from as early as 40 years.

Conclusion

Prostate cancer is one of the common cancers where there is good evidence for a larger genetic component to its etiology, but the genetic models are complex. It is highly likely that the PCa predisposition genes will be polygenic and may be interacting within families. Some PCa predisposition genes are likely to be DNA repair genes (e.g., *BRCA2*) but these may account for only a small proportion of young cases. However, the discovery of high-risk *BRCA2* mutations has led to the first clinical targeted screening trial based on genotype in this disease (the IMPACT study, discussed above), and this trial will serve as a basis for further targeted screening and chemoprevention trials based on genotype as further genes are identified. The lessons learned in IMPACT will be screening uptake in a high-risk male population, the psychological issues of screening men at higher risk of PCa, the utility of PSA in a higher risk population, the identification of new and better biomarkers and the clinical parameters of PCa so identified.

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