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Review Article

HEREDITARY PROSTATE CANCER: CLINICAL ASPECTS

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ABSTRACT

Purpose: We review the current epidemiological and genetic knowledge regarding hereditary prostate cancer, and outline its clinical implications.

Materials and Methods: Published articles on hereditary prostate cancer were identified using the MEDLINE data base.

Results: A risk of prostate cancer, particularly early onset disease, is strongly affected by family history (number of relatives with prostate cancer and their age at diagnosis). A family history of prostate cancer increases the positive predictive value of prostate specific antigen testing and, hence, heredity should always be assessed when deciding whether to perform biopsies in a man with a prostate specific antigen level of 3 to 10 ng./ml. Epidemiological studies indicate that dominantly inherited susceptibility genes with high penetrance cause 5% to 10% of all prostate cancer cases, and as much as 30% to 40% of early onset disease. More than a half dozen chromosome loci that may comprise such genes have been mapped, but as of May 2002 no prostate cancer susceptibility gene of major importance had been cloned. Most likely, environmental factors and comparatively common variants of several other genes affect prostate cancer risk in families with or without multiple cases of the disease. On average, hereditary prostate cancer is diagnosed 6 to 7 years earlier than sporadic prostate cancer, but does not otherwise differ clinically from the sporadic form. As a consequence of the earlier onset, a greater proportion of men with hereditary prostate cancer die of the disease than those with nonhereditary prostate cancer. At present, the only clinically applicable measure to reduce prostate cancer mortality in families with hereditary disease is screening, with the aim of diagnosing the disease when it is still in a curable stage.

Conclusions: Hereditary susceptibility is now considered the strongest risk factor for prostate cancer and has profound clinical importance. The genetic mechanism behind such susceptibility has turned out to be more complex than initially thought, and will probably not be completely understood for many years to come.

KEY WORDS: prostate; prostatic neoplasms; neoplastic syndromes, hereditary; genetic markers

Although familial clustering of cancer was described almost a century ago, it was not until the 1970s that hereditary predisposition was recognized as an important cause of cancer. In the last 2 decades of the twentieth century it was recognized that 3% to 10% of all cancers originating from the breasts, ovaries and colorectum are caused by germline mutations in tumor suppressor genes, and that susceptibility to those cancers is inherited as highly penetrant, autosomal dominant mendelian traits in some families.[1] Familial aggregation of prostate cancer was first reported by Morganti et al[2] in 1956, but the concept of hereditary prostate cancer was not established until 1992, when researchers at The Johns Hopkins School of Medicine in Baltimore published their results from a segregation analysis of 691 men with localized prostate cancer.[3] Their analyses indicated that 9% of the prostate cancer cases in the subjects' families were caused by a rare high risk allele, and as many as 43% of the cases diagnosed before age 55 years. The penetrance of this allele was calculated to be 88% by age 85 years.

In 1996 a locus on the long arm of chromosome 1 that likely comprises such a high risk allele was mapped through a genome wide linkage analysis.[4] The putative prostate cancer susceptibility gene at this locus was named HPC1 (hereditary prostate cancer gene 1). Several other gene loci have been claimed to comprise hereditary prostate cancer genes, but as yet no clinically important prostate susceptibility gene has been identified or cloned.[5–12] The difficulties of cloning the hereditary prostate cancer genes, together with the large number of proposed gene loci, indicate that the genetics of hereditary prostate cancer are more complex than the genetics of hereditary susceptibility to cancer at many other sites. Although the molecular genetics of hereditary prostate cancer are still obscure, there is no doubt that hereditary susceptibility is of profound importance for the development of a substantial proportion of prostatic cancers,[13] and that family history of prostate cancer is a parameter that should be accounted for in clinical practice.

MATERIALS AND METHODS

Articles in this field were identified using the MEDLINE data base. The search was conducted using the following key words in various combinations: prostate cancer, hereditary, familial, genetics, risk, linkage. For all relevant articles identified the search function "Related Articles" was used, which yielded a number of additional articles. The latest MEDLINE search was conducted in October 2001. Epidemiological studies on family history as a risk factor have been reviewed

previously, and only a small number of these are referred to in the present review.[14]

RESULTS AND DISCUSSION

Family history as a risk factor for prostate cancer. Family history is now firmly established as the strongest risk factor for prostate cancer. Following the first report on familial aggregation of prostate cancer in 1956,[2] a large number of epidemiological studies on family history as a risk factor have shown an increased risk of prostate cancer for brothers and sons of men with the disease.[14] The table shows the relationship between family history and prostate cancer risk, with an attempt to adjust the findings of the epidemiological studies for various kinds of bias. It is noteworthy that the risk increases, particularly for early onset disease, for relatives of men diagnosed at an early age.[15,16] Several epidemiological studies have indicated that the risk is greater for brothers than for sons of men with prostate cancer.[17–21] Since there is strong evidence for X-linked inheritance in some families,[7,22] and some evidence for recessive inheritance,[23,24] these findings are likely to be clinically relevant. However, the higher risk for brothers than for sons of men with prostate cancer may also be explained by shared environmental factors and detection bias.

The importance of family history when investigating men with slightly elevated prostate specific antigen (PSA). Contrary to the sensitivity and specificity of screening tests, the positive predictive value varies with the prevalence of the disease in the screened population.[25] The higher the prevalence, the higher the positive predictive value. As a consequence, the risk of prostate cancer for men with a slightly to moderately elevated serum concentration of PSA is substantially higher (that is the positive predictive value of an elevated PSA is higher) for those with a positive family history than for those with no affected relatives. This fact should be considered when one is deciding whether to perform prostatic biopsies in men with a PSA of 3 to 10 ng./ml. In a study by Aprikian et al of 2,968 men referred to a urological department for prostate cancer detection 40% of the 329 patients who reported having a relative with prostate cancer had a positive biopsy compared with 29% of the 2,639 patients who reported a negative family history.[26] Mean patient age, PSA, PSA density and proportion of men with a suspicious digital rectal examination were equivalent in the 2 groups. Similar findings were reported in a screening study conducted in Canada.[18] In a Finnish screening study heredity, PSA and findings on digital rectal examination were the 3 most important factors predicting prostate cancer diagnosis.[27]

Effect of family history of prostate cancer on lifetime risk of clinical prostate cancer

Family History	Relative Risk	% Absolute Risk
Negative	1	8
Father affected at 60 yrs. or older	1.5	12
1 Brother affected at age 60 yrs. or older	2	15
Father affected before age 60 yrs.	2.5	20
1 Brother affected before age 60 yrs.	3	25
2 Affected male relatives*	4	30
3 Or more affected male relatives†	5	35–45

The absolute lifetime risk of clinical prostate cancer for men with a negative family history is derived from Swedish studies, but the figures are approximately the same for other high incidence populations in Northern Europe, North America and Australia. The relative risks represent approximations based on a synthesis of published epidemiological studies, accounting for various kinds of bias. The relative risk of early onset prostate cancer and thereby death from prostate cancer for men with relatives with early onset disease is substantially higher than the risks shown in the table.

* Father and brother, or 2 brothers, or a brother and a maternal grandfather or uncle, or a father and a paternal grandfather or uncle.

† The absolute lifetime risk for mutation carriers is probably 70% to 90% for high penetrance genes such as HPC1.

The increase in positive predictive value is more pronounced if the relative has been diagnosed at an early age or if multiple family members are affected. Thus, assessment of the family history of prostate cancer should always be part of the investigation of men with a PSA of 3 to 10 ng./ml., and the family history should be considered together with other established factors, such as the ratio of free-to-total PSA, PSA density, patient age and so forth, when deciding whether prostatic biopsies should be performed. One should also arrange for a more vigilant followup after negative biopsies in men with a positive family history.

How common is hereditary prostate cancer? Since the hereditary prostate cancer genes have not yet been cloned, the definition of hereditary prostate cancer is still based on the pedigree only. The generally accepted definition includes nuclear families with 3 cases of prostate cancer, families with prostate cancer in each of 3 generations in the paternal or maternal lineage and families with 2 men diagnosed with the disease before age 55 years.[28] Approximately 3% to 5% of prostate cancer cases can be classified as hereditary based on these criteria.[3,29,30] However, because of the difficulty in identifying female mutation carriers, the pedigree has poor sensitivity in detecting families with hereditary susceptibility to prostate cancer. The true proportion of prostate cancer caused by mutations in dominantly inherited susceptibility genes with high penetrance is more likely 5% to 10%.[28,30] Among men with early onset prostate cancer hereditary susceptibility is much more common, and may account for up to one-third of the cases diagnosed before age 60 years and more than 40% of those diagnosed before age 55 years.[3,30]

Prostate cancer susceptibility genes. HPC1 on Chromosome 1q24–25: In 1996 a genome wide search with linkage analysis resulted in mapping of a prostate cancer susceptibility gene to chromosome 1q24–25.[4] This gene, named HPC1, was linked to prostate cancer in one-third of the 79 North American and the 12 Swedish families studied. Several subsequent investigations confirmed the existence of a susceptibility gene at this locus,[10,31–37] but others have failed to demonstrate significant linkage in families with hereditary prostate cancer.[5,22,38–44] Therefore, the proportion of families with hereditary prostate cancer linked to HPC1 is probably substantially less than the initial estimate.

In an analysis of 772 families with hereditary prostate cancer from a large number of centers in North America, Europe and Australia the estimated proportion of those linked to HPC1 was only 6%.[35] Linkage to HPC1 was mainly found in families with male-to-male germline transmission of early onset disease diagnosed in 5 or more family members, with 29% of the families fulfilling these 3 criteria linked. A study showing that allelic imbalance at the HPC1 locus is not common in hereditary prostate cancers suggests that HPC1 may not act as a classic tumor suppressor gene.[45] The HPC1 gene is not likely to be of much importance in the carcinogenesis of sporadic prostate cancer.[45–48]

PCaP on Chromosome 1q42–43: In 1998 a group of French and German researchers published evidence for a second prostate cancer susceptibility gene on the long arm of chromosome 1 (1q42.2–43) based on linkage analysis of 47 families.[5] The putative gene at this locus was named PCaP (predisposing for cancer of the prostate). Three years later, the French researchers published supportive evidence for the importance of this locus in the population of Southern and Western Europe,[43] but with 1 exception,[10] it has not yet been possible to confirm these findings in other populations.[36,37,40–42,44,49]

HPCX on Chromosome Xq27–28: Several epidemiological studies have indicated that the risk of prostate cancer is higher for brothers than for sons of men with the disease, suggesting X-linked or recessive inheritance in some families. Therefore, it was not surprising when a prostate cancer susceptibility gene located on the X chromosome (Xq27–28)

was reported in 1998.[7] The gene, named HPCX, accounted for 16% of the North American hereditary prostate cancer cases analyzed in the original report. HPCX also seems to be a major prostate cancer susceptibility gene in the Finnish population,[7,22] but it has been difficult to confirm linkage in other populations.[41–44,49,50] Lange et al found additional support for this locus among white, but not among black, American families with hereditary prostate cancer.[51]

It should be noted that HPCX cannot be a classic tumor suppressor gene. Tumor suppressor genes, such as the retinoblastoma gene and the BRCA genes, are located at the somatic chromosomes and, according to Knudson's "2-hit hypothesis," 1 copy (maternal or paternal) of the gene carries an inactivating germline mutation, whereas the other copy maintains sufficient action until it gets "hit" by a deleterious mutation in an individual cell, initiating carcinogenesis.[52] Men have only 1 X chromosome, and a germline truncating mutation in any of the genes on that chromosome would make all cells lack the corresponding protein from embryogenesis onward. HPCX mutations seem to be more common in late onset prostate cancer, which may indicate that a dysfunctional HPCX gene acts as a promoter rather than an initiator in prostatic carcinogenesis.[22]

CAPB on Chromosome 1p36: In 1999 a fourth chromosome locus linked to hereditary prostate cancer was reported.[6] Only a small percentage of the families with hereditary prostate cancer who were analyzed were associated with this locus, but in the original study most families with multiple cases of prostate cancer and 1 or more cases of brain tumor were linked to it. Therefore, the putative gene at this locus was named CAPB (cancer of the prostate and brain). Some supportive evidence was found in American[37] and European[53] populations although the locus was not related to brain tumors in the latter group. Other studies have failed to confirm this locus in families with hereditary prostate cancer.[36,41,43]

HPC2 on Chromosome 17p12: In 2000 Myriad Genetics, Inc. (Salt Lake City, Utah) patented a gene located on chromosome 17p12. The gene was named HPC2/ELAC2 because it is homologous to the elaC in Escherichia coli bacteria. This was the first prostate cancer susceptibility gene to be cloned, but most likely it is a rare cause of hereditary prostate cancer. The patent was based on the finding of a germline terminating mutation in men with prostate cancer from only 1 family in Utah.[9]

In addition to this single family with a terminating mutation, another family from Utah was found to have a missense mutation (Arg781His, changing an arginine residue to histidine in the protein) in HPC2 segregating with prostate cancer.[9] A second missense mutation, Ala541Thr, was found to be common in the general population (prevalence approximately 4%), and seemed to increase the risk of prostate cancer by a factor of 2 to 3. Supportive evidence that the Ala541Thr variant is associated with increased risk of prostate cancer was published by 2 American groups.[54,55] However, the results of 2 other American studies[56,57] and 1 Finnish study[58] were negative. In fact, no truncating mutations were found in the HPC1/ELAC2 gene in 93 American[57] or 107 Finnish[58] patients with hereditary prostate cancer, and no genome wide screen has shown significant linkage to this locus. Thus, more studies are needed to define the role of this gene in prostate cancer.

HPC20 on Chromosome 20q13: In 2000 Berry et al published results from a genome wide search indicating that 12% of 162 North American families with hereditary prostate cancer analyzed were linked to a locus on chromosome 20q13.[8] The putative gene at this locus was named HPC20. Additional evidence for this locus was published by Zheng et al.[59] In both studies linkage was more common among patients with later onset disease. Some support, although not statistically significant, was also produced by a third American group,[60] while negative results were published by French researchers.[61]

Why are there so many putative loci? When HPC1 was mapped in 1996, most researchers thought the investigation of hereditary prostate cancer would follow the path of that for hereditary breast, ovarian and colorectal cancers, that is that within a few years HPC1 would be cloned and 1 or 2 additional hereditary prostate cancer genes would be identified. Instead, there have been new loci reported every year, and as of October 2001 only 1 gene (HPC2) of uncertain significance has been cloned. In addition to the aforementioned 6 loci, several other loci that may be of importance in some families with hereditary prostate cancer have been reported, including 4q,[10] 16q23.2[11] and 8p22–23.[12]

Why are there so many putative hereditary prostate cancer gene loci, and why is it so difficult to clone hereditary prostate cancer genes? Partly, the problems are methodological. Prostate cancer is a common disease and linkage studies, as well as attempts to clone mapped genes, are confounded by sporadic cases in families with hereditary prostate cancer. Most studies are performed in the United States, where screening for the disease has greatly increased the detection of sporadic cases and, hence, the number of phenocopies in families with hereditary prostate cancer. Screening is likely particularly common among men with relatives diagnosed with prostate cancer, which further obscures the picture. Furthermore, it is likely that different genes are of importance in different populations. The conflicting results from linkage studies in families with hereditary prostate cancer were reviewed and well analyzed by Ostrander and Stanford.[62] Some of the loci investigated for prostate cancer susceptibility genes may eventually turn out to be artifacts.

Could it be that hereditary predisposition is less important for prostate cancer development than we initially thought? Probably not, but the genetic mechanisms may be more complex than we foresaw. A recent large study of Nordic twins identified the prostate as the site with the greatest proportion of cancers caused by hereditary factors (42%).[13] This high estimate indicates that there are several common genetic polymorphisms (gene variants) or missense mutations (mutations that result in the exchange of only 1 amino acid in the protein) that only moderately increase the risk of prostate cancer and that require additional environmental factors (external or internal, for example endocrine) to result in clinical disease. Currently investigated candidate genes for such genetic variants include the androgen receptor and 5α-reductase type 2 genes,[63] and the CYP17 and CYP19 genes (encoding enzymes in the testosterone metabolism).[64,65] Recessive inheritance may also be important in some families.[23,24]

The small difference in age at onset between hereditary and sporadic prostate cancer (6 to 7 years compared with 20 years in breast, ovarian and colorectal cancers) implies that environmental factors may be of importance in many families with hereditary prostate cancer. Furthermore, there may be as yet unknown genes that modify the expression or penetrance of the prostate cancer susceptibility genes, which could partly explain the difficulties in confirming and cloning the mapped genes discussed previously. Within the next decade it may be discovered that the majority of prostate cancer cases occur in a genetically predisposed minority of the population. This finding could form the basis for a selective screening strategy in the future.

Cancer at other sites in hereditary prostate cancer. Whereas an increased risk of prostate cancer in first degree relatives of men with the disease has been a constant epidemiological finding, studies of associations between prostate cancer and cancer at other sites are conflicting. Although there seems to be a connection between susceptibility to prostate cancer and susceptibility to other cancers, such as brain tumors,[6,66] gastric cancer[34,67] and breast cancer,[34,68] in some families

the results of hitherto published studies indicate that most genes involved in hereditary susceptibility to prostate cancer are relatively site specific. However, this issue cannot be settled until the different genes are cloned and large populations of mutation carriers can be studied.

BRCA1 and BRCA2. Men in families with germline mutations in 1 of the 2 breast cancer susceptibility genes, BRCA1 and BRCA2, are at increased risk for prostate cancer.[69] The estimates of prostate cancer risk in such families are inconsistent, but the relative risk for mutation carriers compared with noncarriers is likely in the range of 2 to 5, with a higher risk for carriers of BRCA2 than BRCA1 mutations.[70–72] Data from Iceland indicate that men with a mutation in BRCA2 are at particularly high risk for poorly differentiated, disseminated prostate cancer.[73] A nuclear family with 5 cases of early onset prostate cancer and 3 cases of breast cancer, all with a truncating mutation in the BRCA2 gene, has been reported from Sweden.[74] Excluding families with multiple cases of breast cancer, germline mutations in BRCA1 and BRCA2 are not likely to be of significant importance as a cause of prostate cancer.[75]

Clinical characteristics of hereditary prostate cancer. A characteristic feature of prostate cancer is that it is commonly multifocal, with an average of 5 apparently independent foci at the time of diagnosis.[76] Multifocality is otherwise a typical feature of hereditary cancer, but the multifocality of prostatic carcinomas is not related to family history.[76] There are no differences between patients with hereditary prostate cancer and those with sporadic prostate cancer regarding tumor grade and pathological stage at diagnosis.[76–79]

Comparing survival between hereditary and sporadic prostate cancer cases is difficult because increased awareness of symptoms and more common participation in screening may result in the earlier diagnosis of hereditary cases, leading to longer survival (lead time bias). Furthermore, it may well be that the clinical characteristics of the disease depend on which susceptibility gene is involved in a family. Most studies have shown similar outcomes for men with sporadic versus hereditary prostate cancer,[77,78,80–84] while some indicate that hereditary disease may be associated with a worse prognosis.[85,86]

The most prominent clinical feature of hereditary prostate cancer is the comparatively early age at onset. Patients from families with hereditary prostate cancer are diagnosed, on average, 6 to 7 years earlier than those with sporadic prostate cancer.[4,30,77,78] As a consequence of the earlier onset, a greater proportion of men with hereditary prostate cancer die of the disease. For example in Sweden prostate cancer is the cause of death in approximately half of all men diagnosed with the disease, but this rate increases to 75% in those with hereditary prostate cancer.[78] The conclusion that can be drawn from available studies is that patients with hereditary prostate cancer should not be treated differently from those of comparable age with sporadic disease, other than that watchful waiting might be a less suitable option for men who have had the painful experience of a having a close relative die of the disease.

Counseling men at high risk for prostate cancer. More and more male patients at urological outpatient departments are concerned about possible hereditary predisposition to prostate cancer. These men should be offered basic genetic counseling, including an explanation of the genetic mechanisms of autosomal dominant and X-linked traits, and notification of risk in absolute (for example 35% to 45%, or 1 in 2 to 3, for men in families with hereditary prostate cancer) and relative terms (for example 4 times the risk for men in the general population; see Appendix). Many unaffected men in families with hereditary prostate cancer overestimate their lifetime risk of the disease and, therefore, such information will often reduce concerns about cancer risk.[87] Members of families with hereditary cancer syndromes usually have experienced close relatives dying of cancer, often at an early age. Awareness of being at high risk for cancer is often associated with anxiety or depression, and it is of paramount importance to address the psychological aspects of cancer predisposition when counseling this group of patients.[88]

How can we reduce prostate cancer mortality in the population at high risk for the disease? In the future it may be possible to replace mutated susceptibility genes or to reduce the risk of disease by chemoprophylaxis, but presently these therapeutic modalities are only vague shadows on the horizon. Prophylactic radical prostatectomy might be an option when presymptomatic genetic testing becomes feasible and gene carriers with extremely high risk (70% to 90%) of prostate cancer can be identified. However, the side effects of radical prostatectomy will probably restrict its use even among these men. Therefore, at present, and most likely for the next few decades, early detection, aimed at diagnosing the disease when it is still in a curable stage, will be the standard recommendation when counseling men at high risk for prostate cancer.

Screening. Screening for prostate cancer is a controversial issue. Mammography screening has proved to reduce breast cancer mortality in randomized studies,[89] but screening for prostate cancer with PSA and digital rectal examination has no such scientific basis. Randomized screening studies are in progress in many European countries, but results with regard to mortality will not be available for another half decade.[90] However, there is no doubt that regular PSA testing of asymptomatic middle-aged men reduces the number diagnosed with locally advanced and metastatic disease.[91]

Although screening for prostate cancer is not generally recommended in Sweden, the Swedish national guidelines for the management of hereditary cancer syndromes, which will be published later this year, include a recommendation for annual PSA testing and clinical examination in men who have 2 or more close relatives with prostate cancer. The risk of clinical prostate cancer developing before age 70 years in these men is approximately 15%, which is more than 5 times the risk for those with a negative family history. The risk increases to 30% to 45% if a relative is diagnosed before age 70 years.[15]

Compared with screening in the general population, screening in a select high risk group defined by family history has an improved cost-to-benefit ratio. The extremely high incidence of prostate cancer dramatically decreases the number of men required to be screened to detect 1 case. Also, the positive predictive value of PSA is higher, leading to a smaller proportion of healthy men with false-positive test results. In addition, the earlier age at onset of hereditary prostate cancer, with the associated higher mortality, increases the potential gain in survival by curative treatments and decreases the proportion of men who will be treated for tumors that would not have progressed to symptomatic systemic disease within their lifetime. Furthermore, men in families with hereditary prostate cancer are often concerned about their increased risk, and it is of substantial psychological importance to these individuals that something be done to reduce their risk of dying of cancer.[87]

On the other hand, those men in high risk families who do have elevated PSA values due to benign prostatic diseases are a major concern. Unlike false-positive mammograms, which can ultimately lead to a radical surgical biopsy that proves the benign nature of the lesion, an elevated PSA only signals an increased risk of a malignant tumor somewhere in the target organ. We can never tell a man with elevated PSA values that he has no cancer, regardless of how many prostatic biopsies we obtain. For men at high risk for prostate cancer who have experienced a close relative dying of metastatic disease such a situation is severely distressing. Hence, the risk of false-positive PSA tests should be discussed with the patient before he is offered regular screening.

The American Cancer Society recommends that screening among men at high risk for prostate cancer be initiated at or before age 45 years.[92] In families with hereditary prostate cancer it is reasonable to screen for the disease starting at least 5 years before the earliest age at diagnosis in the family, and at least 10 years before the age at which metastatic disease appeared. For men with persisting normal PSA values screening can be terminated at approximately age 70 years since the risk of dying of prostate cancer is low.[93]

The Swedish guidelines recommend annual PSA testing and digital rectal examination. Although the latter does not significantly increase sensitivity compared with PSA testing alone,[94] the physical examination and personal contact with the physician during the consultation are likely of psychological benefit. It is also important for these men to have an opportunity to discuss their cancer risk, and to be informed about advances in research, for example presymptomatic genetic testing and diagnostic screening. Therefore, this group of men is probably better managed by urologists than by general practitioners or others.

It is important to be aware of the increased positive predictive value of PSA in this high risk population. Men with a PSA of 3 ng./ml. or higher should undergo biopsy, and if the results are negative they should undergo repeat biopsy or reexamination at short time intervals.

Presymptomatic genetic testing. During the second half of the 1990s several cancer susceptibility genes were identified and cloned, making presymptomatic genetic testing possible in many cancer prone families. The aim of such testing is to identify mutation carriers, who should be offered prophylactic treatment or intensive surveillance, and noncarriers, who can be assured that their cancer risk is not higher than that in the general population. Since hereditary cancer susceptibility is caused by germline mutations, testing is performed on leukocyte DNA from an ordinary blood sample. If a germline mutation causing a defect (usually truncation) in the protein of a cancer susceptibility gene is detected in an affected individual, his or her relatives may be tested to determine whether they are carriers of that mutation. Presymptomatic genetic testing for susceptibility to common cancers is now generally applied in families with multiple cases of breast and ovarian cancers, in which the genes BRCA1 and BRCA2 are analyzed,[95] and in families with colon cancer, in which DNA mismatch repair genes are analyzed.[96]

Presymptomatic genetic testing has important psychological, medicolegal and ethical consequences.[97,98] It is not only those who have been identified as gene mutation carriers who need support following genetic testing. In a study of members of families with breast cancer, those who declined testing were the ones most likely to react with depressive symptoms.[99] Adverse psychological reactions ("survivor's guilt") may also occur in those with normal test results.[100] Therefore, testing should always be preceded by thorough education and counseling, and written informed consent.[101] In addition, there should be active followup after counseling for genetic testing, regardless of whether testing was actually carried out.

Within a few years, some of the prostate cancer susceptibility genes may be cloned, making presymptomatic testing for mutations in these genes possible. The interest in genetic testing is high among men with a family history of prostate cancer and, therefore, practicing urologists should be prepared to provide basic information about genetic testing to these men in the near future.[87,102,103] However, the large number of genes involved in prostate cancer susceptibility, and the probable importance of environmental and additional genetic factors that modify cancer risk, will make genetic analyses complicated. In many, if not most, families no mutation will be found that can be definitely associated with an extremely high prostate cancer risk. Therefore, presymptomatic genetic testing in families with hereditary prostate cancer probably will not be as important as it is in families with hereditary breast, ovarian and colorectal cancers.

CONCLUSIONS

Epidemiological studies indicate that dominantly inherited susceptibility genes with high penetrance may cause 5% to 10% of all prostate cancer cases, and as much as 30% to 40% of early onset disease. Furthermore, an even larger proportion of cases is likely attributable to genetic variants that only moderately increase prostate cancer risk. As a consequence, men with a family history of prostate cancer have a significantly increased risk of the disease, particularly if a relative has been diagnosed at an early age or if multiple family members have been affected. Since the prevalence of a disease affects the positive predictive value of screening tests, men with an increased PSA value and a family history of prostate cancer are more likely to have cancer develop than are those with the same PSA value and a negative family history. Therefore, family history should always be assessed and accounted for when deciding whether to perform biopsies in men with a PSA of 3 to 10 ng./ml.

Hereditary prostate cancer is diagnosed, on average, 6 to 7 years earlier than sporadic prostate cancer. Although there do not seem to be other important differences in the clinical characteristics of hereditary and sporadic disease, the earlier age at onset of hereditary prostate cancer results in as many as 75% of affected men dying of the disease if it is not diagnosed early.

The need for genetic counseling will increase as public awareness of prostate cancer and hereditary cancer syndromes increases. All urologists should be able to offer basic counseling, including appropriate risk notification and information about available measures to reduce the risk of dying of prostate cancer. At present, primary prevention, such as chemoprophylaxis or gene therapy, is not available for men at high risk for prostate cancer. Although screening using PSA and digital rectal examination has not yet been proved to reduce prostate cancer mortality, the balance between costs, side effects and the potential benefits of screening are improved when applied to a high risk population. Therefore, annual screening should be offered to men with 2 or more close relatives diagnosed with prostate cancer. However, increased PSA values due to benign prostatic disease are particularly problematic in this high risk population, and this issue should be discussed with patients before screening is commenced.

Several chromosome loci that are likely to comprise dominantly inherited prostate cancer susceptibility genes have been pinpointed, and presymptomatic genetic testing may be available in the near future. However, due to the large number of genes involved, testing will be complicated and it will often not be possible to identify a relevant mutation that can separate individuals at extremely high risk from those who are at average risk for prostate cancer.

The genetic mechanisms behind hereditary susceptibility to prostate cancer have turned out to be remarkably difficult to unravel, most likely because they are more complex than in many other hereditary cancer syndromes. The currently available data suggest that prostate cancer risk in families with or without multiple cases of the disease is modulated by a number of genes and also by environmental factors. Even if the number of studies published annually in this field has grown rapidly during the last decade, we have only just begun to imagine what the picture will be like when the puzzle is finally pieced together.

ADDENDUM

After this review was accepted for publication, a letter was published in Nature Genetics, which proposed the RNASEL

gene on chromosome 1q24–25 as a candidate gene for HPC1.[104] RNASEL encodes a protein with antiviral and pro-apoptotic activities. The authors reported on 2 families with hereditary prostate cancer in which mutations (1 truncating and 1 missense) segregated with prostate cancer. In 6 other families linked to HPC1 no mutation in RNASEL was found. Additional studies are needed before any firm conclusion can be drawn regarding the relationship between RNASEL and HPC1.

APPENDIX: ISSUES TO BE ADDRESSED WHEN COUNSELING MEN WITH FAMILY HISTORY OF PROSTATE CANCER

Brief orientation regarding principles of hereditary susceptibility to cancer
Estimation of individual's risk of prostate cancer in absolute and relative terms
Risk of prostate cancer in general population
Principles and practice of screening for prostate cancer
Risk for unaffected men of having elevated PSA
Genetic testing (not yet available)

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