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GENETIC DETERMINANTS OF PROSTATE CANCER: A REVIEW

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Background. In prostate cancer, early detection and appropriate treatment remain key approaches. But given the constantly increasing incidence, prostate cancer ethiopathogenetic determinants are a current focus of attention. Although the development of this cancer is influenced by both environmental and genetic factors which are as yet ill-defined, genetic studies have revealed gene abnormalities which may be specifically associated with the risk of prostate cancer: changes in genes for the androgen receptor, RNAseL, ELAC2, MSR1, BRCA 1 and 2, HPCX, KLF6, HPC20 and fusion genes, e.g. TMPRSS2-ERG). Despite differing research results from molecular biological studies, these techniques can assist in earlier diagnosis enabling timely initiation of treatment.

Methods. Methods and literature: MEDLINE search was performed to collect both original and review articles addressing prostate cancer and genetic risk factors using key words genetics, prostate cancer and risk.

Conclusions. A number of potential genetic risk factors/markers has been identified which may in near future contribute to earlier diagnosis of prostate cancer so that earlier treatment can be started. Despite many promising data we have found differing results and therefore we suppose further research should be conducted to achieve more precise conclusion. This review focuses on current knowledge of the genetic factors affecting the development of prostate cancer.

INTRODUCTION

Prostate cancer (PC) is now one of the most serious oncological diseases in men with an incidence higher than that of all other solid tumours. Currently, it is the second cause of cancer mortality worldwide[1]. However, while the incidence has been rising continuously since the 1980s when Prostate-Specific Antigen (PSA) testing was introduced into clinical practice, the mortality has remained roughly the same. It was PSA testing that led to an important shift towards the diagnosis of earlier prostate cancer stages (the so called stage migration) and thus better patient prognosis. Before the "PSA era", the majority of prostate carcinomas were diagnosed on digital rectal examination or histologically from prostatectomies (transurethral resection or suprapubic prostatectomy). Today we diagnose more than 70% of PCs from elevated PSAs and the diagnosis is thus made up to 10 years earlier than in the past. The screening not only refers to the time factor. It also refers to the biological potential of the disease as we detect cancers with a lower malignancy (lower histopathological grading and lower cancer staging). On the other hand, a higher prevalence of aggressive cancers is affected by the recommendations for evaluation of prostate cancer grading (Gleason score) made at the Uropathologists Conference ISUP in 2005[2,3]. According to the National Cancer Institute (USA, programme Surveillance, Epidemiology and End Results) 192.280 new PC cases in the year 2009 with a current mortality of 27.360 cases were estimated in the USA. From data for the year 2005, in the Czech Republic we estimated 100,2/100.000 and 28,39/100.000 cases for incidence and mortality, respectively (in absolute numbers the incidence and prevalence in Czech Republic is 5094 and 1443 men, respectively)[4].

RISK FACTORS FOR PROSTATE CANCER

While it is acknowledged that PC is a multifactorial disease, no precise proven cause has been adduced. Although, an enviromental effect on the development of PC is assumed, an important, possibly predominant role is played by genetic predisposition. Differences between PC incidence and mortality in white and Afroamerican men for example, testify to this (156 resp. 25 in white vs. 248 resp. 59 in Afroamerican men /100 000 men)[1].

Enviromental factors include animal fat, alcohol, history of vasectomy, smoking, obesity, statin and nonsteroid anti-inflammatory drug medication, vitamin D and E and mineral intake (calcium, selenium, zinc) and sexual activity. However, the conclusions of a large number of studies on these causative risk factors as either protective or detrimental differ[5]. Androgens, oestrogens, insulin, IGF

(insulin-like growth factor) and other hormones lie on the borderline of enviromental and genetic factors – levels can vary according to individual genetic predisposition and external conditions (hormone substitution, obesity, comorbidities)[6,7].

GENETICS AND PROSTATE CANCER

Generally, oncological disease is caused by multiple gene mutations occurring during cell senescence (due to physical, chemical or biological mutagens). These mutations happen at several levels simultaneously. Such changes are common in healthy cells and do not necessarily lead into malignant transformation. Only if the reparation processes are unable to eliminate the existing malignant cells, does unregulated growth and proliferation take place where among other processes, apoptosis is suppressed. If such cell change or damage occurs in a germ cell, the changed information is transferred onto descendants in a direct line. Typical for this kind of disease transfer in affected families is greater frequency of particular diagnoses, disease onset is earlier, it is bilateral, multifocal or more aggressive than in the normal population (Table 1). Apart from mutation theory, current emphasis is on stem cell theory as explanatory of the pathogenesis of a number of diseases and not only cancer. For genetically determined diseases we can reveal these changes using the methods of molecular genetics (e.g. polymerase chain reaction, fluorescence in situ hybridisation, genome sequention etc.)

Table 1. Examples of genetically determined cancers.

Bilateral neurinoma of the acoustic nerve
Familial adenomatous polyposis of colon
Familial or bilateral breast or ovarian cancer
Hereditary clear cell and papillary renal carcinoma
Retinoblastoma
Wilms's tumour
Familial melanoma
Familial prostate cancer
Multiple endocrine neoplasia (MEN I, II)
Multiple cancer disease (breast, ovarian and non-small cell lung cancer)

Prostate cancers can be divided for practical purposes into three groups – hereditary, familial and sporadic. More than 85% of all prostate cancers are sporadic and only 10–15 per cent cancers are genetically determined. We are able to establish genetic factors with varying degrees of probability. In analysis of population studies, a higher incidence of PC was found in first line relatives[8,9] (Table 2). The appearance of a high risk disposition allele for PC is more frequent in men with cancers that were diagnosed at a younger age (43% of men younger than 55, 34% of men younger than 70 and 9% of men younger than 85)[10,11]. Sporadic prostate cancers occur in men with a negative family history. Familial PC affects two or more men in one family while true hereditary prostate cancers affect three or more men in one family in three subsequent generations or two men aged 55 or younger.

Table 2. Relation of family history and risk of prostate cancer (according to Bratt[9]).

Prostate cancer history in family	Relative risk	Absolute risk (%)
No	1	8
Father or brother	2	15
Father or brother younger than 60 years	3	20
Father and brother	4	30
Hereditary prostate cancer	5	35–45

Meta-analyses of 33 epidemiological studies evaluating familial risk of prostate cancer have shown that the relative risk of prostate cancer in a man with a brother or father with PC is 3.4 and 2.2, respectively. This risk is higher if there are more affected men in the first line than in second line[12,13].

Not only a family history of prostate cancer but also breast/ ovarian cancer increase the risk for men in a given familial line. In such case the relative risk is 1.7 and in the case of incidence of PC together with breast or ovarian cancer, the risk is 5.8 but results from other studies differ[14–16].

Segregate studies have found a mostly autosomal dominant heredity in patients with sporadic and familial prostate cancer. Only in a small group of patients is heredity autosomal recessive or X-linked (gonosomal). We talk about "prostate cancer susceptibility genes" (see below). In this model, 97% of patients with this genetic predisposition will develop PC at the age of 85 compared with only 10% of men without this genome. These genes are also involved in 65% of prostate cancers diagnosed before age of 65[17,18]. Wide epidemiological studies on monozygotic and dizygotic twins have also yielded fruit. The most extensive study resulted from a database with nearly 16.000 twins (World War II. veterans born in the USA between 1917–1927). Prostate cancer was diagnosed in 1009 men and the incidence in monozygotic and dizygotic twins was 27.1 and 7.1%, respectively[19]. These results were also confirmed in Gronberg´s study of Swedish twins[20].

BIOLOGICAL BEHAVIOR OF FAMILIAL AND HEREDITARY PROSTATE CANCERS

Studies have compared the clinical and pathological features of sporadic and hereditary prostate cancers in men referred for PC treatment. Clinical and pathological

staging, serum PSA, postoperative progression of PSA and cancer specific mortality were evaluated. Kupelian et al presented the findings of 1038 men treated with radical prostatectomy or radiotherapy. The patients were divided into two groups – those with positive and negative familial history. Survival without biochemical progression after 5 years in men with and without positive familial history was 52% and 29%, respectively[21], although the results from other centers are discordant. John Hopkins Hospital group evaluated 94 men with familial prostate cancer against 562 men with sporadic cancer treated by radical prostatectomy. Over 65 months there was no difference in pathological features or progression interval[22]. Hanlon[23] retrospectively evaluated 920 men after radiotherapy without neoadjuvant hormonal treatment where 97 of the men fulfilled the criteria for familial or hereditary PC. Although the follow-up was relatively short, there were no differences in terms of frequency or time to biochemical failure. Similar results were presented by Gronberg in Swedish men[24], by Herkommer and Roupręt[25,26].

ANDROGEN RECEPTOR AND GENES OF STEROID HORMONE METABOLISM

Epidemiological studies show that Scandinavian countries have constantly the highest incidence of PC. In contrast, PC incidence in Asian men living in Asia is the lowest in the world. However, the incidence rapidly rises when Asians move e.g. to the USA supporting the theory of the relationship of PC and life-style. The PC prevalence in Afroamericans is significantly higher than in white men living in the same area. Further, more Afroamericans than Caucasian men have worse staging and PC grading as well as a more aggressive disease course[27]. One explanation for this is the different genetic equipment specially in the androgen receptor (AR) gene. This gene is of great importance and the focus of research interest because of its physiological and pathological functions in the prostatic cell. The AR gene is located on the short arm of chromosome X (Xq11–12). This locus is one of the most conservative regions of the human genome. Therefore only a minimum of mutations occur in this region[28,29]. The size of the gene is 90 kbp and AR consists of 918 amino acids. The AR comprises transactivation domain, DNA binding domain and ligand binding domain. There is also an activation region responsible for ligand independent receptor activation. After receptor activation it acts upon appropriate target regions on the DNA chain (androgen responsive elements) and as a result, the expression of information coded in androgen-dependent genes (e.g. PSA, growth factors EGFR, VEGF, IGF, KGF, ARA and many others)[30].

The variability in the AR gene length is determined by polymorphism in the N-terminal region. The number of CAG base triplet (polyglutamin) and GGC base triplet (polyglycin) repetition in the first exon of the AR gene is substantially lower in afroamerican men than in caucasians. The normal number of polyglutamin repetition is 8–35 and most men have 21 repetition. With a lower than 21 repetition, polyglutamin repetition might be connected with higher prostate cancer risk, earlier onset of disease and a more aggressive form, due to stronger binding of ligand and its long-lasting hyperstimulation of the androgen receptor (afroamericans, white and asian men have 18, 21 and 22 repeats, respectively). And conversely, a greater number of polyglutamin repeats (more than 40) leads to alteration of the androgen receptor and its coactivator (with a lower fertility or Kennedy disease as a consequence). The number of glycin repeats can vary from 10–30 but the impact of abnormal repeat count on prostate cancer is still a matter of research in contrast to polyglutamin-chain length where we have much more evidence for a relationship with prostate cancer development[31–35]. In localised prostate cancers, androgen receptor gene mutations can be found only rarely (in around 1%) but are present in 30–45% of metastatic or hormonal resistant prostate cancers[36].

In accord with genetic predisposition for PC data, the role of the 5α-reductase type II gene (SRD5A2) is also a matter of debate. Its polymorphism plays an important role in androgen metabolism in prostate cells. It is presumed that a larger number of dinucleotid repeats in this enzyme increases its enzymatic activity with consequently increased transformation of testosterone to dihydrotestosterone (DHT). On the other hand, data meta-analysis has not convincingly confirmed a higher risk of prostate cancer in this situation[37]. Cunningham et al analyzed genetic variation in a total of 25 genes involved in androgen and estrogen metabolism and found that gene polymorphisms of AKR1C3, NQO1 and GSTT1 were weakly associated with familial PC[38].

GENES AND LOCI ASSOCIATED WITH HEREDITARY PROSTATE CANCER

As mentioned above, 85% of PCs are sporadic and only 15% are familial or hereditary. It was the much higher prevalence and earlier onset of this cancer in some families that led to extensive genome studies to reveal prostate cancer susceptibility genes or locuses similar to high risk genes in breast and ovarian cancer – BRCA1 and BRCA2. The International Consortium of Prostate Cancer Genetics was organized to provide systematic research in this field. The aim was joint cooperation, sharing research data and preparation of metaanalyses[39]. To date, a series of studies have identified putative genes very probably related to PC and, other genes are speculated (Table 3)[7,40–43]. Of all tested candidate genes for prostate cancer, the most important is gene RNAseL in locus HPC1, gene ELAC2 in locus HPC2, gene MSR1 on chromosome 8, gene BRCA2, BRCA1 and others[44]. Although the Human Genome project was completed more than 10 years ago, there are more and more other locuses mapped and termed chronologically (HPC1-HPC20) as well as gene mutations found with possible association to PC development and progression (e.g. KLF6, PTEN, MAD1L1 and others)[45].

Table 3. Genes related to prostate cancer development.

Localisation	Candidate gene/locus	Remark
1q25.3	RNaseL/ HPC1	Age younger than 65 years, higher Gleason score, advanced cancer at time of diagnosis; strongest relationship with PC in families with higher than 5 affected men Affects induction of apoptosis and susceptibility to infection
17p11	ELAC2	Unknown function
8p22–23	MSR1	Initiation of inflammation; affects induction and course of infection
Xq27–28	HPCX	Higher risk of PC in men with affected brother than with affected father
20q13	HPC20	Higher age at PC diagnosis
17q21	BRCA1	More frequent in younger men
13q12–13	BRCA2	Function in DNA reparation

Hereditary Prostate Cancer 1

This is probably the most important locus related to prostate cancer development. It is located on chromosome 1q24–25 and a gene at position 1q25.3 is RNAseL encoding an endoribonuclease. This enzyme is important in the immune response of the organism to viral infection (degradation of single-stranded RNA together with INF α), in apoptosis induction, cell cycle and cell differentiation regulation. Autosomal dominant hereditary is typical for RNAseL and this gene has high penetration. This means that a carrier of this mutant variant has a high risk of prostate cancer development)[46].

Men with this predisposition are found to be of lower age (<65), have more aggressive cancer (according to Gleason score) which is more often locally advanced or even metastatic. Detailed genome analysis in 91 families affected by PC in the USA and Sweden showed that in up to 35% of cases it was exactly in the locus for RNAseL where the mutation occurred. Mutations or polymorphisms of this gene are thought to be related not only to abnormal immune reaction to RNA viral presence but also increased risk of familial prostate cancer although the results of studies may differ in details (e.g. Eelese et al conclude that the importance of RNAseL in hereditary PC is only marginal but its significance increases in cases of more than four men in a family and in contrast – correlation of HPC1 with PC in Afroamericans and Hispanic men has been unambiguously declared)[41,47–50]. Despite primary convincing results claimed. The Jewish community of Ashkenasi support the relationship between PC and RNAseL gene mutation but this connection was not later confirmed[51,52].

There are recent works supporting very probable association between endoribonuclease RNAseL impaired function and the presence of xenotropic murine leukemia virus-related virus (XMRV virus) whose DNA was identified in 6% of PC (XMRV protein was identified in 23% of PC whereas the expression was primarily in malignant cells). PCs with this virus embodied more often aggressive biological behaviour[53]. Other candidate genes in the localization of HPC1 include the gene for cyclin-dependent kinase PCTAIRE, protooncogene TRK and the gene for human laminin B2. It is speculated that absence or loss-of-function mutation of these genes may promote the development of PC[30].

Hereditary prostate cancer 2, X and 20

Hereditary prostate cancer 2 is another locus on chromosome 17p11 with a suspected link to PC. A protein coded by a gene at this locus (ElaC homolog protein 2 or Zn-phosphodiesterase) has been defined. However, the direct relationship between mutation and polymorphism remains unproven[54,55]. Hereditary prostate cancer X is one of few locuses on chromosome X suspected to have a relationship to hereditary PC. It is localised in position Xq27–28. Among others, located here is a complex of SPANX genes which are probably connected to other types of cancer[56]. It is the gonosomal type of inheritance presumptive of an atypical mode of transmission – studies have revealed higher relative risk of PC for men with a brother affected by prostate cancer than for men with an affected father. It is presumed that HPCX is responsible for 16% of hereditary carcinomas[57,58]. The locus for HPC 20 is on chromosome 20q13. It is speculated that if any, it plays a role in men with PC diagnosed at a higher age[59].

The location of many of tumour-suppressor genes is characteristic for the short arm of 8p chromosome. Inactivation of these genes may be linked with carcinogenesis not only in prostate but also in lung, liver and bowel. The physiological function of Macrophage Scavenger Receptor 1 (MSR1) is a modulation of interaction between foreign cell and macrophages, cell adhesion and its phagocytosis. However meta analysis of the data has failed to reveal any clear correlation between the locus for MSR1 and the hereditary risk for PC[60]. As mentioned above, the use of Breast Cancer Antigenes (BRCA) 1 and 2 is a common practice when examining genetic predisposition for breast and ovarian cancer. Detection of mutations in these genes in men is connected with higher risk

of hereditary prostate cancer. The presence of BRCA 1 gene is more often related to men younger than 65 years but in the case of the BRCA 2 gene, age does not play any important role although in younger men the mutation of BRCA 2 makes the risk even higher. BRCA 1 gene is localised on 17q21 and plays a crucial role in keeping the genome stable by controlling the cell cycle and by reparing impaired DNA. The localisation of BRCA 2 gene is 13q12–13 and it has similar function to BRCA 1.

FUSION GENES AND OTHER ALTERATIONS IN SPORADIC CANCERS

The circumstances under which the genetic information in prostate cells changes, do not automatically lead to prostate cancer. These changes occur frequently during the lifetime and it is repair mechanisms what can reveal such mutation and further how relevant the mutation is and whether it can be repaired. In the contrary case, the mutated cell can lead to clonal expansion with all possible consequencies. The problem is that these sporadic carcinomas count for up to 85% of all PCs although there is only a minimal risk of cancer transfer to the next generation in the case of sporadic PC. Genetic changes can be similar to those in hereditary cancers caused by not only single-nucleotide mutation but by gene translocation. The importance of this form of mutation was demonstrated in the fusion of genes TMPRSS2 to ERG[61]. TMPRSS2 is a serine protease whose significance has not been defined in detail. It is present in prostate cells and influences their physiological and pathological processes. Fusion of TMPRSS2 to transcription factor ERG and others, e.g. ETV1, 4 ceteris paribus may increase the malignant potential of cells and cause cancerogenesis. According to several studies, prostate cancers with this fusion are more aggressive and have a worse prognosis although the results of other studies do not support this hypothesis[62,63]. The loss-of-function mutation of KLF 6 (Krüppel-like factor 6 at chromosome 10p15) is another genetic change which can lead to cell proliferation deregulation. Indeed, it has been proven that KLF 6 mutation is present in up to 55% of sporadic prostate cancers although the original presumption of importance in hereditary PCs has not been confirmed[31,64]. Among other factors we can list mutations in genes c-Myc, E-cadherin, NKX31 and in tumour supressor genes PTEN, p53 and RB[65].

CONCLUSION

Despite extensive research, prostate cancer from an ethiopathological point of view remains a barely examined disease. With further developments in the methods of molecular pathology we are offered new possibilities of early diagnosis, determination of disease prognosis and prediction of treatment results. Given its current global incidence and sociological impact, prostate cancer remains of central concern to urologists, pathologists, oncologists and increasingly, molecular biologists and geneticists, albeit it may be some time before the results of the latter are applicable to clinical practice.

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