Abstract. – Genetic factors and their interactions with environmental conditions and internal microenvironment influence the prostate cancer (PC) development, so that gene expression couldn’t strictly occur on the basis of reductionist determinisms of DNA causality but should also conform to multifactorial and stochastic events, moreover, considering the pre-RNA alternative splicing-mediated multi-protein assembling mechanisms. Nevertheless, after age and ethnic background, the strongest epidemiological risk factor for PC is a positive family history. However, apart from RNaseL-, ElaC2-, MSR1-genes, there are not other identified high-risk genetic variants which might be considered responsible for hereditary PC, moreover suggesting that familial PC is a genetically heterogeneous disease, many gene loci rather than a specific major susceptibility gene predisposing to it. Gene-environment interactions play a crucial role in cancer development especially when low penetrance genes, such as in case of genetic polymorphisms, are the major players. Several epidemiological studies show, in some families, a possible, either synchronous or metachronous, association of other tumors (breast, brain, gastrointestinal tumors, lymphomas) with PC, thus suggesting a common genetic background. As far as the role of androgen metabolism and androgen receptor (AR)-related genes in the development of familial PC is concerned, a small number of either guanine-guanine-cytosine (<16) or cytosine-adenine-guanine (<18) repeats appears to increase the AR activity, resulting in a raising PC risk. Regarding the expression of both androgen and estrogen receptor-related genes in sporadic and hereditary PC, the immunohistochemistry findings show that the percentage of AR-positive cancer cells is higher in hereditary PC than in sporadic forms, whereas the mean number of estrogen-α-receptor-positive stromal cells is higher in sporadic PC rather than in that hereditary. As for 5-α-steroid-reductase-2 gene, the dinucleotide thymine-adenine repeated 18 times on the last exon, confers an increased PC predisposition, as it is mainly shown in African-American populations. Also VDR gene, that is a component of ligand (steroid)-dependent nuclear transcription factor superfamily, shows various polymorphisms which appear to be associated with PC risk. Except an earlier age of onset, no anatomo-clinical and tumor progression peculiarities between hereditary and sporadic PC have been generally identified. Indeed, tumor progression and metastasis, both in hereditary and sporadic PC, are mainly influenced by a variety of biochemical and immune-mediated tumor microenvironmental conditions rather than by the hereditary genetic factors, thus gene expression associated with invasive ability representing a newly acquired genetic variant rather than a selection of pre-existent gene abnormalities in PC cells. It’s questionable whether genetic testing of unaffected men of hereditary PC families might be actually useful. Nevertheless a suitable counselling must be proposed. Family history and/or gene profiling-guided preventive strategies for men at high risk of familial PC, range from dietary to drug measures. Cancer chemopreventive approaches may include 5-α-reductase inhibitors, histone deacetylase inhibitors, antioxidants, non-steroidal anti-inflammatory drugs, cholesterol-lowering statins, vitamin D analogues.

Key Words: Inheritance, Prostate cancer, Microenvironment, Tumors, Urology.

Introduction

In the developed Western countries, prostate carcinoma (PC) is the most frequently diagnosed malignancy in men and the third most common cause of cancer-related mortality in North America. Its incidence and mortality vary considerably among different ethnic groups, with high prevalence in African-American men.
Prostate carcinoma is a multifactorial disease whose etiology ranges from genetic factors to environmental conditions and internal microenvironment (“milieu intérieur”). Nevertheless, after age and ethnic background, the strongest epidemiological risk factor for PC is a positive family history, several aggregation analyses and linkage investigations showing that, on the one hand, some alleles, with high penetrance, may confer a dominant inheritance susceptibility to PC with rise in cases of the disease within individual families (hereditary PC), and, on the other hand, many polymorphisms, with low penetrance, may influence, by integrating environmental conditions, the frequency of both familial and sporadic disease. In this regard, a distinction must be made between hereditary and familial forms, considering that hereditary transmission, compatible with Mendelian inheritance criteria, is demonstrated only in 5% of the cases with PC family history whereas familial PC accounts about 13-25% of cases. Indeed, families with hereditary PC may be identified by having three or more affected first-degree relatives (father, son, brother) within the nuclear family or, differently, a frequency of PC in three successive generations, or, at least, two affected relatives before the age of 55 years, given that genetic susceptibility is proportionally more shown in young patients rather than in old. Familial aggregation of PC which don’t fulfill such criteria are defined as familial forms, that, more properly, are characterized by at least two affected first-degree relatives. Anyway, the risk of PC is about two-fold in the first-degree relatives of diseased men, it increasing proportionally to number of diseased relatives and their decrease in age at the diagnosis, so that the risk of developing a PC is assessed 8.5 for men with both first- and second-degree affected relatives.

Hereditary Form

The definition of hereditary PC is mainly based on the family history (pedigree). Despite a strong support for a significant role of inherited genetic variants in PC etiopathogenesis, however few indisputable high-risk genetic abnormalities have been shown in cases fulfilling the hereditary PC epidemiological criteria, thus suggesting that even the hereditary PC could be a genetically heterogeneous disease. Many gene loci rather than any major susceptibility gene predispose to it, likely interacting not only reciprocally but also with environmental conditions, that, however, affect more strongly the sporadic PC initiation.

Hereditary transmission may be autosomal dominant – through the mother or the father – and even X-linked – through the mother to her sons who will not transmit the susceptibility to their own sons –, and by the last way the disease jumping regularly one generation with subsequent its under-estimation. Autosomal dominant high-penetrant gene-related transmission is usually associated with disease onset at younger age while that recessive chromosome X-linked is characterized by late-onset disease.

The first chromosome locus associated with hereditary PC was 1q24-25 and its putative gene was named HPC1 (hereditary prostate carcinoma 1), which, in turn, was identified with RNaseL gene (Table IA), involved in interferon-activated apoptosis for virus-infected cells. Indeed, recent studies show that RNaseL gene mutations are responsible for PC particularly in men with γ-retrovirus-mediated prostate infections, among which especially the xenotropic murine leukemia virus-related γ-retrovirus (XMRV). Actually, forty percent of hereditary PC patients homozigous for a mutation in RNaseL are positive for XMRV whereas this virus is rarely detected in sporadic PC specimens, such finding meaning as a true breakthrough in the pathogenesis of PC. Polymorphic variants within RNaseL gene are associated with raised risk of hereditary PC.

Other strong candidate susceptibility genes are ElaC2/HPC2 (locus 17p11.2) and MSR1 (macrophage scavenger receptor 1) (Table IA). Also a mutation in a gene on 8q24 locus should appear to increase the risk of PC by 60%, but it is more relevant to pathogenesis of familial and sporadic PC. An indeterminate number of weak candidate susceptibility loci have been suggested to be involved in hereditary PC (Table IB). However, PC high risk alleles, that are able to drive a lifetime penetrance of at least 66%, have a frequency unlikely above 2-3% of the cases, whereas PC low risk alleles may have a more frequent impact on sporadic PC. With regard to PC susceptibility locus 1q42.2-43 (PCAP, prostate cancer predisposing), the prostate carcinoma tumor antigen-1 (PCTA-1), that is located within such chromosomal region, is not a PC high risk gene while it could make one’s low risk contribution to sporadic PC, but it must be thoroughly explored.
Table I. Genes involved in hereditary PC.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Encoding function</th>
<th>Encoded protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Strong candidate susceptibility genes involved in hereditary prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• RNase L</td>
<td>1q24-25</td>
<td>Encodes RNaseL</td>
<td>RNaseL, endoribonuclease located in cytoplasm and mitochondria.</td>
</tr>
<tr>
<td>(Ribonuclease L)</td>
<td>HPC1</td>
<td>– Interferon-activated, it plays an antiviral and proapoptotic role</td>
<td></td>
</tr>
<tr>
<td>• ElaC2</td>
<td>17p11.2</td>
<td>Encodes a zinc phosphodiesterase</td>
<td>Zinc phosphodiesterase, located in the nucleus.</td>
</tr>
<tr>
<td></td>
<td>HPC2</td>
<td>(ElaC protein 2) – Displays tRNA 3’-processing endonuclease activity (removal of a 3’ trailer from precursor tRNA), thus inducing tRNA maturation</td>
<td></td>
</tr>
<tr>
<td>• MSR1 (macrophage scavenger receptor)</td>
<td>8p22-23</td>
<td>Encodes membrane glycoproteins</td>
<td>Glycoprotein membrane, macrophage scavenger receptor type-I and -II, Involved in the arterial wall deposition of cholesterol during atherogenesis and in endocytosis of low density lipoproteins</td>
</tr>
</tbody>
</table>

B) Weak candidate susceptibility genes (low risk alleles)

1p35-36 (CAPB), 1q42-43 (PCAP), 16q23, 17q22, 20q13 (HPC 20), Xq27-28 (HPCX)

Although hMMR (human mis-match repair) gene alterations should predispose to urogenital and gastrointestinal inherited cancer in the field of a malignancy susceptibility syndrome named Lynch syndrome or hereditary non-poliposis colorectal carcinoma (HNPCC), specific inherited susceptibility to PC does not exist in such syndrome, whereas hMMR gene changes (inactivating mutations of hMLH1 and LMSH2) often occur in sporadic PC.

Apart from younger age at diagnosis – the onset of hereditary PC is on average six years earlier than sporadic form – there are not other phenotype characteristics that might be associated with hereditary cases, the clinical course being otherwise no different in comparison with sporadic forms.

Familial Form

The familial PC reflects, much more than hereditary form, the confluence of genetic predisposition with environmental risk factors (diet, pollution, smoking behaviour, ionizing and non-ionizing radiations, etc) in the field of stochastic events.

Single nucleotide polymorphisms (SNPs) within three adjacent regions at 8q24 have been recently identified to be connected with familial PC risk, providing evidence that SNPs play a significant role in such PC form. Particularly, 8q24 chromosomal band, where maps c-MYC gene regulating cell proliferation and apoptosis, is commonly gained in PC. Variability at 8q24, especially at rs6983267, is associated with high risk of aggressiveness potential patterns at diagnosis, besides the familial status, but not with a family history of mammary cancer or other malignancies.

As well as 8q24, seven novel PC predisposition loci – genetic variants on chromosomes 3, 6, 7, 10, 11, 19 and X – have been just confirmed by an international genome-wide association study (Practical consortium) since explaining 16 percent of the PC familial risk.

Further genome-wide analyses lead to the identification of other potential candidate chromosomal loci, such as 22q12.1 (CHEK2 gene) and 12p13.1 (CDKN1B gene), thus confirming the genetic heterogeneity of the susceptibility to PC in its different ethno-geographic-dependent familial forms. Particularly, the CHEK2 gene significance consists in encoding for cell-cycle-checkpoint kinase 2, a mediator of either DNA repair- or apoptosis-mediated cell response to DNA damage.

Even germline sequence variants of LZTS1 suppressor gene (8p22-23) may be associated with PC familial risk.
Familial Clustering of Prostate Cancer Associated with Other Tumors

Several epidemiological analyses show, in some families, a possible, either synchronous or metachronous, association of different tumors – breast, brain, gastrointestinal tumors, lymphomas – with prostate carcinoma, thus suggesting a common genetic background that can cause a PC risk rise in men with first- or second-degree relatives suffering from other malignancies. In families with PC, diagnosed before the age of 55 years, and breast carcinoma, changes of BRCA2 gene (breast carcinoma 2 gene, locus 13q12-13) have been identified, particularly at exon 11 level, which coincides with region involved in the risk of association with ovarian carcinoma. The PC risk increases 1.4 times if a man is first- or second-degree relative from a woman with a breast carcinoma.

A possible association of PC with brain tumors is borne out by the localization, at locus 1p36, of a CAPB (prostate and brain cancer) common susceptibility gene.

A significant rise in gastric carcinoma risk has been shown in pedigrees from PC patients with diagnosis of the disease before the age of 55 years; nevertheless, in such patients, no association is found between PC and germline mutations of E-cadherin gene, which predisposes to particular forms of familial gastric carcinoma.

Some PC families have a co-occurrence of pancreas adenocarcinoma, three chromosomal regions – 2q, 16q, 17q – harboring common potential susceptibility genes.

Role of Adrogen Metabolism and Androgen Receptor-Related Genes in the Development of Familial Prostate Carcinoma

In the prostate tissue, testosterone (T) is metabolized, by the 5-α-steroid-reductase-2 (srd5α-2), into dihydrotestosterone (DHT), that is 2.5 times more active than T on the nuclear membrane androgen receptors (AR). As far as srd5α-2 gene (locus 2p22-23) polymorphisms are concerned, the dinucleotide thymine-adenine (TA) repeated 18 times on the last exon (TA18 alleles), confers an increased PC predisposition, as it is found in the African-American populations. A variant of exon 1 – valine (val) to leucine (leu) replacement at codon 89 – confers to val-val homozygous individuals, mainly represented in African-American populations, an increased PC susceptibility risk, whereas the genotype leu-leu, that is more frequent in Asian populations, appears to have protective effects.

The androgen activity is primarily mediated through nuclear membrane AR that also acts as a ligand-activated transcription-factor, inducing the expression of target genes which control both proliferation and differentiation of prostate cells. Indeed, upon androgen binding, the AR dimerizes and translocates into the nucleus, where it binds specific DNA sequences of target genes, to initiate the transcription. The transcriptional domain of AR protein-N-terminal region is encoded by AR gene exon 1 that contains certain GGC (guanine-guanine-cytosine) and CAG (cytosine-adenine-guanine) repeats. A small number of either GGC (<16) or CAG (<18) repeats (shorter repeats) appears to increase the AR activity, resulting in a raising PC risk.

The implication of chromosome Y in PC is well shown, considering that the loss of chromosomal Y segment is the most common chromosomal alteration which might be identified in PC tissue. As far as chromosome Y-specific gene changes are concerned, SRY – sex-related gene on chromosome Y – is down-regulated in PC and, because SRY-gene acts as negative regulator of AR, the loss of chromosome Y results in increase in PC growth. Nevertheless, the findings of recent studies are against the role of Y chromosome in the initiation or outcome of PC.

By analysing the expression of both androgen and estrogen receptor-related genes in sporadic and hereditary PC, the immunohistochemistry findings show that the percentage of AR-positive cancer cells is higher in hereditary PC than in sporadic form, whereas the mean number of estrogen-α-receptor-positive stromal cells is higher in sporadic versus hereditary PC, thus suggesting that a typical pattern of steroid hormone receptors is associated with hereditary susceptibility to PC. Otherwise, the role of estrogens during the prostate tumorigenesis is still unclear.

Sporadic Form

Although multiple genes might influence sporadic PC risk, most current attempts to identify the related gene-variants are based on single-gene approaches.

Three single nucleotide polymorphisms (SNPs) at 8q24 and two at 17q (17q12, 17q24.3) have been associated with sporadic PC. Nevertheless, a cumulative association of these five SNPs plus...
family history is part of familial PC. Each SNP independently can increase PC risk 1.1 to 1.65, so men with four or five of these SNPs are exposed to a PC risk 4-5 times higher than subjects without them. If a positive family history is added, as a sixth high risk factor, to such SNPs, the risk ratio for PC approaches 10 times, however this last dramatic condition involving only 1.4% of the cases.

Among the SNPs contributing to sporadic PC, particularly vitamin D receptor (VDR) gene polymorphisms appear to play a significant role in its development. VDR gene (locus 12q12), that is a component of ligand (steroid)-dependent nuclear transcription factors superfamily, shows various polymorphisms which appear to be associated with PC risk. In prostate cells, 1,25-(OH)2 vitamin D binds to nuclear VDR, thus forming a complex that, on the one hand, regulates the transcription of several genes involved in cell differentiation and growth, particularly by promoting the expression of IGFBP-3 (insulin-growth factor binding protein-3) that inhibits proteins involved as a risk factors for PC and, on the other hand, modulates the androgen metabolizing genes. Nevertheless, some metaanalyses on the most studied VDR-SNPs have shown that such variants unlikely can bring about the susceptibility to PC, at most impacting on the cancer progression and on the risk of recurrence.

Even an adenine to guanine substitution (rs925013) in the promoter of PSA (prostate specific antigen) gene has been found to be associated with sporadic PC risk.

About the polymorphisms concerning genes involved in carcinogens metabolism, the homozygous genotypes for null-allele of glutathione-S-transferase-theta 1 (GSTT1) gene, locus 22q11.23, by causing a decrease in detoxification of arylamines and aromatic hydrocarbons, can influence the risk of PC development as well as an higher expression of the NAT-2, N-acetyltransferase-2 gene, locus 8p22, NAT-2 enzyme activity inducing a slow acetylation of nitrosamines and aromatic amines in comparison with NAT-1 gene, that, instead, characterizes the rapid acetylator phenotype.

HPC2/ElaC2 gene, besides to be recognized as hereditary PC susceptibility gene, may present some polymorphisms that are associated with sporadic PC. PC risk-related gene polymorphisms are much more common in the population rather than it might be high-penetrance cancer susceptibility gene; particularly, threonine (thr) allele at level 541 in HPC2/ElaC2 plays a significant role in the sporadic PC predisposition in Japanese populations.

Gene activity profiling studies show that gene expression differs between the peripheral zone (PZ) and transitional zone (TZ), thus influencing the growth and differentiation of prostate tissue. PZ genes, such as GDF 15 (growth differentiation factor 15), strongly influenced by p53, and TARP (T-cell receptor gamma chain alternate reading frame protein) result overexpressed in PC, while TZ genes, such as Wnt, Wingless-type, and forkhead family-related genes (FOXF1, FOXF2), the last with antimitotic/Wingless-type properties, are highly expressed in benign prostatic hyperplasia.

**Pathological Outcomes and Clinical Features of Hereditary/Familial Prostate Cancer**

There are conflicting points of view regarding whether hereditary PC might have different pathological outcomes and clinical features in comparison with sporadic form, but considering various key-data – PSA at diagnosis, biopsy findings, biochemical progression, age at surgery, free survival rates – the difference is not statistically significant. Actually, except an earlier age of onset (on average, 5 to 8 years sooner for the hereditary forms), no anatomo-clinical and cancer progression peculiarities between hereditary and sporadic PC are usually identified, even the prognosis and post-operative clinical features resulting entirely similar in both forms. Only a study focused on HPC 1 locus (1q24-25, RNaseL gene)-related hereditary form shows a prevalence of less differentiated and advanced tumors with bad prognosis compared to sporadic forms. Recent research indicates that men with a PC affected relative have well differentiated PC in comparison with subjects without affected relatives but that appears to be caused by earlier and more pursuing screening in men with family history, hence a detection of PC in early stage and, consequently, with more favorable characteristics. Even the clinicopathological features and long-term oncological outcomes are equivalent after radical prostatectomy in both hereditary and sporadic PC patients.

Apart from the genetic abnormality-related initiation phase (carcinogenesis), also in hereditary PC, as well as in sporadic form, tumor progression...
and metastasis are mainly influenced by a variety of biochemo-physical and immune-mediated tumor microenvironmental conditions rather than by the hereditary genetic factors, thus turning-out to be similar in both forms. Various growth factors and cytokines, that are produced and secreted by microenvironmental stromal cells, are able to promote some genetic impairments that induce non-invasive prostate cancer cells to acquire an aggressive phenotype, thus gene expression associated with prostate cancer invasive ability representing a newly acquired genetic variant (particularly, mutant-p53 and defective p63) due to interactions between tumor cells and surrounding microenvironment rather than a selection of pre-existent gene alterations in PC cells.

An increased expression of FOXP3 transcription factor in both the tumor infiltrating Tregs (immune suppressive T regulatory cells) and tumor cells themselves has been recently found in different invasive-metastatic malignancies. Therefore metastatic PC is molecularly, in some ways, distinct from the primary tumor as well as progression from hormone-sensitive to hormone-independent PC growth involves some additional genetic and epigenetic alterations. Otherwise, during tumor progression, prostate cancer cells may regain pluripotent stem cell-like behavior through a dedifferentiation process or may themselves be malignant stem cell clones, anyway they needing sustaining influences from the micromilieu to display their stem-ability patterns. An exciting field of research, regarding a long-term success of cancer treatment strategy, includes some current trials of cancer stem cell eradicating therapy.

However, some chromosome 8q24 regions, besides their recent identified association with familial PC risk, play also an important role in influencing PC advanced disease. In fact, the frequency of overexpression of the 8q24 locus, in fluorescence in situ hybridization analyses, raises from PIN, prostatic intraepithelial neoplasia, to PC aggressive phase. The translocation of ETS (E26 transcription specific) factor (ERG/ETV1) to TMPRS-2 (transmembrane protease serine-2, locus 21q22), androgen-responsive promoter region – thus constituting the TMPRS-2/ERG genetic rearrangement with androgen-dysregulated expression of ERG – appears to represent a PC progression genetic alteration rather than a carcinogenesis initiation event.

Even transcript level of miRNA (microinterfering RNA) targets becomes lower in adrogen-refractory PC than in adrogen-dependent PC, miRNA-gene abnormalities, such as deletion and downregulation of microgenes miR15 and miR16 (locus 13q14), affecting the post-transcriptional machinery of “gene silencing” (post-transcriptional gene knock-out) with following increase in oncogene expression.

Because no anatomo-clinical differences are actually identified between hereditary and sporadic PC, it follows that the management of inherited forms must conform to current guidelines for PC.

Concluding Remarks

Genetic factors and their interactions with environmental conditions (occupational, carcinogen pollution, ionizing and non-ionizing radiations, infections, diet, lifestyle) and internal microenvironment (Claude Bernard’s concept of “milieu intérieur”), influence the PC etiopathogenesis, so the gene expression couldn’t strictly occur on the basis of reductionist determinisms of DNA causality but should also conform to multifactorial and stochastic events (DNA stochastic extension), moreover considering the intriguing role of pre-mRNA alternative splicing to produce a variety of proteins from the same gene’s expression as adaptive response to several chemical and physical stressing agents. Particularly, gene-environment interactions play a crucial role in cancer development especially where low-penetrance genes, such as some genetic polymorphisms, are the mayor players. The considerable difference in frequency of PC between men in western developed countries and Asian populations has been attributed to remarkable differences in lifestyle. So, the western type diet rich in saturated fatty acids rather than in vegetables, has been considered to play a potentially significant role in the incidence of PC in migration studies, many Asian ethnic group that are transmigrated in developed western countries leaving behind their traditional lifestyle to adopt the western style.

 Whereas the aggregation of PC in some families suggests the involvement of susceptibility genes (monogenic inheritance in hereditary PC), in both familial and sporadic forms, instead, the genetic factors should be polygenic, chiefly polymorphism-dependent. Apart from RNaseL-, ElaC2-, MSR 1 genes, there are no other identified high-risk genetic changes which indis-
putably might be responsible for hereditary PC (table 1A), epidemiological analyses indicating that highly penetrant susceptibility genes cause about 5-8% of all cases of PC and up to 40% of PC early-onset.

In the clinical field, a thorough family history is the most important tool of analysis to assess the hereditary familial risk of PC. A family history is particularly useful when managing men with PSA level range of 1.5-10 ng/mL. Family history must concern how many and which male relatives have been affected by PC and at what age and stage the disease has been identified as well as how many relatives have suffered from other tumors (especially, from breast, ovary, brain neoplasias and, less significantly, from Lynch syndrome yet regarding NSM2 gene only).

For men at high risk of hereditary PC, PSA-, EPCA (early prostate cancer antigen)-, PCA3 (prostate cancer antigen 3/DD3 gene)-testing should be considered 5 years before the earliest age at diagnosis in relatives or, at least, one decade before the age at that a metastatic PC has appeared in the family or, anyway, no later than at age 50 years or, as suggested from American Cancer Society, at the age of 40 years or earlier, with subsequent proper check timing (Table II). Sarcosine (N-methyl derivative of the aminoacid glycine) plays a critical role for PC invasive progression and disease aggressiveness, certainly not for early detection of PC.

It’s questionable whether genetic testing of unaffected members of hereditary PC families might be actually useful, just considering the wide genetic heterogeneousness of hereditary PC without as yet any indisputable high-risk allele. Nevertheless towards unaffected first- and second-degree male relatives, a suitable counselling must be proposed.

Family history- and/or gene profiling-guided preventive strategies for men at high-risk of familial PC range from dietary to drug measures (Table III). Cancer chemopreventive approaches, particularly at epigenetic level, could be by now available. Histone deacetylase (HDAC) inhibitors are able to induce an increased histone acetylation and Sp3 transcription factor that binds to the promoter region of P21WAF1 gene, thus resulting in elevated p21 protein expression with cell cycle regulating modulation. Dietary constituents, such as isothiocyanates (e.g., sulforaphane, found in broccoli sprouts/ cruciferous vegetables) and allyl-organosulfur compounds, present in garlic, are metabolized to mercaptan derivatives acting as HDAC inhibitors in prostate tissue as well as in other organs.

As far as preventive treatment with finasteride is concerned, a decrease in PC incidence, by ap-

### Table II. PSA check timing for men at high risk of hereditary prostate cancer.

<table>
<thead>
<tr>
<th>PSA range</th>
<th>Check timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 ng/mL</td>
<td>Biennial as long as PSA levels remain below</td>
</tr>
<tr>
<td>1-2 ng/mL</td>
<td>Annual and, in addition, digital rectal exploration</td>
</tr>
<tr>
<td>&gt;2 ng/mL</td>
<td>Quickly sequential checking together with testing PSA-density, – velocity and – free/total ratio. In problematic cases, prompt resort to PCA3 testing and, if need be, to the biopsy</td>
</tr>
</tbody>
</table>

### Table III. Candidate targets for preventive measures for men at high-risk of hereditary prostate cancer.

| Steroid hormone | – 5-α-reductase inhibitors (finasteride, dutasteride) |
| Oxidative DNA damage (ROS, reactive oxygen species) | – Phyto-estrogens (soy products) |
| – Antioxidants: thiocyanates, isoflavonoids, polyphenoles, lycopene, |
| – Trace-elements (selenium, zinc), vitamin E |
| – Nutraceuticals from curcuma, papaya, pineapple, soy, tomato |
| Cell proliferation/apoptosis | – Nonsteroidal anti-inflammatory drugs (acetylsalicyl acid, COX2 inhibitors) |
| – Colesterol-lowering statins |
| – Vitamin D analogues |
| Epigene | – Histone-deacetylase inhibitors (vorinostat) |
| – DNA-methyltransferase inhibitors, against hypermetilation of tumor suppressor genes (azacitidine, decitabine) |
| Gene | – Looking to the future, corrective replacement of tumor suppressor genes (in gametes ex vivo) and/or post-transcriptional oncogene silencing by miRNAs |
approximately 25%, among treated men, has been shown, however without reduction of the risk for high-grade carcinoma. Moreover, it has been supposed that 5-α-reductase inhibitors might suppress hormone-dependent cancer cells whereas poorly differentiated hormone-refractory cell clones may develop, although at low PSA levels, after a longer trial than 7 years that such research was running. Nevertheless, more recent updates of PCPT, Prostate Cancer Prevention Trial, appear to suggest a reduction of the risk of clinically significant PC even including high-grade tumors, together with proposing the hypothesis that 5-α-reductase inhibitors might improve detection of high-grade PC, due to decreased prostate volume, with possible resorting to transrectal ultrasound-elastography, a technique that allows to measure the elastic properties of the prostate gland. Interestingly, also from REDUCE (Reduction by Dutasteride of prostate Cancer Events) trial are emerging hopeful prospects for an effective dutasteride-induced PC prevention. Otherwise, no specific studies on protective effects of such compounds towards men with family PC risk appear to be so far available. Several adverse effects of long-term preventive use of these drugs, such as decreased libido and ejaculatory dysfunction, must be weighed up.

Non-steroidal anti-inflammatory drugs (acetylsalicylic acid, COX2-inhibitors) and cholesterol-lowering statins, such as simvastatin, inhibit prostate epithelial cell growth, thus suggesting their chemopreventive potential towards PC high-risk.

Looking to the future, oncopreventive approaches could straigh concern the hereditary genetic abnormalities, either by corrective replacement of defective genes in gametes or by post-transcriptional gene expression inhibition resorting to micro-interfering RNAs or, even, by oncogene inactivation through antisense oligonucleotides. On this subject, much intriguing work is as of now under way in the field of gene therapy for PC. In addition to the large variety of gene delivery vehicles – either viral or non-viral vectors such as liposomas, polymers, nanoparticles – gene oncotherapy includes, on the one hand, some antiproliferative strategies, ranging from both prodrug suicide- and antisense-gene therapy to immunotherapeutic gene technologies (delivery of genes encoding for specific cytokines) and, on the other hand, the corrective replacement of tumor suppressive genes.

References

5) Bratt O. What should a urologist know about hereditary predisposition to prostate cancer? BJU Internat 2006; 99: 743-748.


