Molecular epidemiology of prostate cancer: androgens and polymorphisms in androgen-related genes

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Abstract

In most western countries prostate cancer is the most commonly diagnosed non-skin cancer in men. Despite its high morbidity and mortality the etiology of prostate cancer remains obscure. The involvement of androgens has been examined extensively in prostate carcinogenesis but the results of most epidemiological studies remain inconclusive. This review focuses on current perspectives of androgen levels and polymorphisms in androgen-related genes. Racial differences in genetic polymorphisms that have a role in the biosynthesis and metabolism of androgens may partly account for racial differences in prostate cancer risk. Reasons are also given for inconsistent results in molecular epidemiological studies and insights and directions for future research are discussed. The development of a polygenic model for prostate cancer, incorporating multiple loci from the individual genes, may maximize the chance of identifying individuals with high-risk genotypes, resulting in better preventive, diagnostic, and therapeutic strategies.

Introduction

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of death as a result of cancer in men in the United States and many other western countries. There is a large variation in prostate cancer incidence rates between racial/ethnic groups, highest among Africans, intermediate among Caucasians, and lowest among Asians (1). Although the reasons for this large disparity in risk are mostly unclear, population differences in androgen levels and dietary factors have been implicated as possible explanations.

Steroid hormones, particularly androgens, appear to play a major role in the development of prostate cancer, but their precise role is not clear (2, 3). Prostate cancer regresses after anti-androgen therapy, and administration of testosterone induces prostate tumors in laboratory animals (4, 5). However, epidemiological studies addressing the role of androgens in prostate cancer have produced conflicting results. The search for genetic markers of prostate cancer susceptibility has revealed an increasing number of genetic polymorphisms that may have a role in the metabolism of testosterone and other androgens.

Biosynthesis and metabolism of androgens

Androgens are steroid hormones that induce the differentiation and maturation of the male reproductive organs and the development of male secondary sex characteristics. In men, androgens are formed in the testes and the adrenal gland whereas they are metabolized in the prostate and skin. Androgen production is regulated by the hypothalamic–pituitary–gonadal axis. Gonadotropin-releasing hormone is secreted by the hypothalamus in pulses, thus stimulating luteinizing hormone (LH) secretion from the pituitary gland. LH acts on Leydig cells in the testis to induce androgen production.

Testosterone, the major male androgen in the circulation, and dihydrotestosterone (DHT), the principal androgen in tissue and the most potent androgen, are the two most important androgens in adult males. In blood, roughly 44% of testosterone is bound with high affinity to sex hormone-binding globulin, 54% with low affinity to albumin, and only 1–2% of testosterone exists in a free, bioavailable state. About 25% of the DHT in the circulation is secreted by the testes, while most arises from conversion of testosterone in peripheral tissue in a reaction catalyzed by the
enzyme 5α-reductase (Fig. 1). In humans, two 5α-reductase isoenzymes have been identified. The type 1 enzyme (encoded by the SRD5A1 gene) is expressed mostly in newborn scalp, skin, hair, and liver, whereas the type 2 enzyme (encoded by the SRD5A2 gene) is localized primarily in androgen target tissue, including genital skin and the prostate gland (6).

**Androgenic action within the prostate**

Both testosterone and DHT exert their androgenic effects in the prostate through the androgen receptor (AR) protein (Fig. 2). The AR is normally associated with heat shock proteins in an inactive state. Androgen binding induces dissociation from heat shock proteins, hyperphosphorylation, conformational changes, and dimerization of the receptor. The ligand–receptor complex then translocates to the cell nucleus where it binds to specific DNA sequences termed androgen-responsive elements located within the promoters of androgen-responsive genes. In conjunction with AR-associated proteins (AR coactivators (ARA)) and other transcription factors, the AR is then able to up- or down-regulate the transcription of several genes. \textit{In vitro} studies have shown that certain AR coactivators, such as ARA54, ARA55, ARA70, ARA160, p160, breast cancer susceptibility gene 1, amplified in breast cancer 1 (AIB1) and cortisol binding protein can enhance AR transcriptional activity several-fold (7, 8).

Activation of the AR leads to complex proliferative, apoptotic, and angiogenic events. Androgens enhance expression of cyclin-dependent kinases 2 and 4, as well as induce down-regulation of the cell cycle inhibitor p16 (9). The overall effect of androgens in cells expressing AR is an increase of cyclin-dependent kinase activity and stimulation of cells to enter the S phase of the cell cycle, thereby inducing cellular proliferation.

**Androgens and prostate cancer**

Androgens play an important role in normal and hyperplastic prostate growth. Both testosterone and DHT have been shown to induce prostate adenocarcinomas in experimental rat models (5). Several epidemiological studies have compared the serum levels of androgens in prostate cancer cases with those in healthy subjects in either case control or prospective designs (10–21). In most of these studies the serum concentrations of testosterone and DHT were measured to assess the role of androgens in prostate cancer. Although only one study reported a statistically significant association between serum levels of testosterone and prostate cancer (16), several studies found a suggestive but statistically non-significant association between prostate cancer and the serum levels of testosterone and DHT (10, 12). Circulating testosterone levels in African–American and European–American pregnant women during the first trimester of pregnancy have also been compared (22). African–American women had 47% higher levels of testosterone, suggesting that in this high-risk population the fetus is exposed to higher concentrations of androgens before birth (22).

In most epidemiological studies the failure to show an association between androgen levels and prostate cancer risk can be partly explained by methodological limitations, including difficulty in making reliable measurements of circulating hormone levels in an epidemiological setting, small sample size, small differences (usually 10–15%) in mean serum levels of hormones between cases and controls, and large intra- and interassay laboratory variations in serum hormone assays (2, 3, 23).

The most important limitation in epidemiological studies assessing serum levels of androgens is whether circulating levels of androgens reflect androgenic activity within the prostate gland since the metabolism of testosterone to DHT occurs mainly in the prostate, not in the circulation. If serum levels of androgens do not reflect the levels of DHT in tissue, it is difficult to interpret results from serological studies (2, 3). However, no epidemiological studies have investigated levels of hormones in prostate tissue. It is also unclear as to whether cumulative exposure to androgens over a lifetime or exposure at certain points in life is more relevant in prostate carcinogenesis (2, 3).
Genetic polymorphisms

The search for genetic markers of disease susceptibility often focuses on a gene, based on the properties and metabolic pathways of its protein product. Thus, genes involved in androgen biosynthesis and metabolism cascade have been identified as possible modifiers for prostate cancer (24). Racial differences in genetic polymorphisms that have a role in the metabolism of testosterone and other androgens may partly account for racial differences in prostate cancer risk. Several candidate genes are discussed in this review.

CYP17

CYP17 is located on chromosome 10 (10q24.32) and encodes the cytochrome P450c17α enzyme (25). This cytochrome mediates both 17α-hydroxylase and 17,20-lyase activities at key points in the testosterone biosynthesis cascade in gonads and adrenals (25). The 5′ untranslated promoter region of the CYP17 gene contains a polymorphic T to C substitution that gives rise to A1 (T) and A2 (C) alleles (26). An early study suggested that the A2 allele creates an additional Sp1-binding site (CCACC box) in the CYP17 promoter region (26). Subsequently, Nedelcheva Kristensen et al. (27) did not document Sp1 binding at this polymorphic site or within the promoter region of CYP17 in general, while Lin et al. (28) found that Sp1 is an essential factor for CYP17 transcription in human adrenal NCI-H295A cells. Overall, evidence that the A2 allele increases androgen levels is weak and inconsistent (29–31).

Molecular epidemiological studies have presented contradictory results concerning a potential role of CYP17 in prostate cancer (Table 1). Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (31–36). However, other investigations have been apparently inconclusive (37, 38) or have even reported that the A1 allele may increase the risk of prostate cancer (31–36). Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (31–36). Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (31–36). Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (31–36). Some studies have indicated that the A2 allele may be associated with an increased risk of prostate cancer (31–36).

SRD5A2

SRD5A2 is located on chromosome 2 (2p23) and encodes the steroid 5α-reductase type 2 enzyme. This membrane-bound enzyme catalyzes the irreversible conversion of testosterone into the main prostatic androgen, DHT. The binding affinity of DHT to the prostatic AR is five times higher than that of testosterone (42). Ross et al. (43) demonstrated that young Japanese men have lower 5α-reductase activity than young Caucasian–American and African–American men. Similarly, Wu et al. (44) reported that the DHT to testosterone ratio was highest in African–Americans, intermediate in whites, and lowest in Asian–Americans, corresponding to the respective risk of developing prostate cancer in these groups.

Certain SRD5A2 polymorphisms may encode for 5α-reductase enzyme variants with different activities, probably due to altered mRNA stability (45). Makridakis et al. (46) reported a missense substitution in the SRD5A2 gene, which replaces valine at codon 89 with leucine (V89L). This substitution results in an almost 30% reduction in 5α-reductase activity both in vitro and in vivo (46). In another variant of the SRD5A2 gene (47), an alanine residue at codon 49 is replaced with threonine (A49T). This missense mutation increases steroid 5α-reductase activity fivefold in vitro (47). Thus, these polymorphisms might alter DHT levels and consequently the risk of prostate cancer. A polymorphism in the 3′ untranslated region has also been reported, with different numbers of TA dinucleotide repeats (48). A substitution of glutamine for arginine at codon 227 (R227Q) is already known but is very rare in Asian descent subjects where this polymorphism has been studied (49). The biochemical evidence for a putative relationship of SRD5A2 polymorphisms with androgen levels is controversial (30, 49–51).

Molecular epidemiological studies have presented seemingly contradictory results concerning a potential role of the V89L (35–37, 49, 50, 52–55), A49T (36, 37, 47, 49, 54–56) and TA repeat (37, 49, 55, 57) polymorphisms in prostate cancer susceptibility (Table 1). A meta-analysis has excluded a role for the V89L polymorphism in conferring susceptibility to prostate cancer and suggests that the A49T and TA repeat polymorphisms may have a modest effect on prostate cancer susceptibility, but bias and chance findings cannot be excluded (58). The only study investigating the role of the R227Q polymorphism found no association with prostate cancer risk (49).

AR

The AR is expressed in all histologic types and stages of prostate cancer. The AR gene, which is located on the X chromosome (Xq11.2–12), is highly polymorphic. Two CAG (coding for polyglutamine) and GGN (coding for glycine) microsatellite repeats are present in exon 1 of the AR gene, residing in the transactivation domain. Expansion of the CAG repeat length in the AR N-terminal region results in a structurally altered protein with reduced transcriptional activity (59, 60). An alternative molecular mechanism was raised by Choong et al. (61) who observed that CAG repeat expansion in the first exon of the AR gene reduced AR mRNA and protein levels. However, the biological role of GGN trinucleotide repeats is less clear.

Several reports (37, 62–80) have investigated the role of CAG and GGN repeats in predisposition to breast cancer. A recent meta-analysis suggests that the A1 allele may increase the risk of prostate cancer (39, 40). A recent meta-analysis suggests that the A1 allele may increase the risk of prostate cancer (39, 40). A recent meta-analysis suggests that the A1 allele may increase the risk of prostate cancer (39, 40). A recent meta-analysis suggests that the A1 allele may increase the risk of prostate cancer (39, 40).
Table 1 Studies of polymorphisms in androgen-related genes and prostate cancer risk.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Study (Reference)</th>
<th>Racial descent</th>
<th>Prostate cancer (no.)</th>
<th>Controls (no.)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17</td>
<td>MspAI</td>
<td>Lunn et al. 1999 (35)</td>
<td>European, African</td>
<td>108</td>
<td>167</td>
<td>A2A2 vs A1A1 1.70 (0.70–4.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wadelius et al. 1999 (39)</td>
<td>European</td>
<td>178</td>
<td>160</td>
<td>A1A1 vs A2A2 1.61 (1.02–2.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gsur et al. 2000 (33)</td>
<td>European</td>
<td>63</td>
<td>126</td>
<td>A2A2 vs A1A1 2.80 (1.02–7.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Habuchi et al. 2000 (40)</td>
<td>Asian</td>
<td>252</td>
<td>333</td>
<td>A1A1 vs A2A2 2.57 (1.39–4.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kittles et al. 2001 (32)</td>
<td>European</td>
<td>600</td>
<td>804</td>
<td>A2A2 vs A1A1 1.17 (0.85–1.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yamada et al. 2001 (36)</td>
<td>African</td>
<td>71</td>
<td>111</td>
<td>A2A2 vs A1A1 2.80 (1.00–7.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chang et al. 2001 (38)</td>
<td>European</td>
<td>105</td>
<td>210</td>
<td>A2A2 vs A1A1 2.39 (1.04–5.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latil et al. 2002 (34)</td>
<td>European, African</td>
<td>590</td>
<td>538</td>
<td>A2A2 vs A1A1 1.04 (0.57–1.91)</td>
</tr>
</tbody>
</table>

| SRD5A2 | V89L | Febbo et al. 1999 (50) | European | 592 | 807 | LL vs VV 0.84 (0.57–1.24) |
|        |     | Lunn et al. 1999 (35) | European, African | 108 | 167 | LL vs VV 1.00 (0.30–2.90) |
|        |     | Margiotti et al. 2000 (55) | European | 108 | 121 | VV/LL vs LL 0.35 (0.09–1.32) |
|        |     | Nam et al. 2001 (52) | European | 158 | 162 | VV vs LL 2.76 (1.17–6.50) |
|        |     | Latil et al. 2001 (37) | European | 226 | 156 | LL vs VV 2.30 (0.98–5.40) |
|        |     | Yamada et al. 2001 (49) | Asian | 105 | 210 | LL vs VV 1.37 (0.70–2.71) |
|        |     | Hsing et al. 2001 (49) | Asian | 268 | 495 | LL vs VV 0.88 (0.53–1.47) |
|        |     | Pearce et al. 2002 (53) | European, Asian, African | 921 | 1294 | LL vs VV 1.15 (0.85–1.54) |
|        |     | Soderstrom et al. 2002 (54) | European | 176 | 161 | VV vs LL 1.42 (0.70–2.89) |

| A49T | (TA)n | Makridakis et al. 1999 (47) | European, African | 388 | 461 | AT/TT vs AA European: 2.50 (0.90–7.40) |
|      |     | Margiotti et al. 2000 (55) | European | 108 | 121 | AT vs AA 7.7 (0.39–150.54) |
|      |     | Latil et al. 2001 (37) | European | 226 | 156 | AT vs AA 0.80 (0.26–2.42) |
|      |     | Mononen et al. 2001 (56) | European | 449 | 811 | TT vs AA 1.04 (0.62–1.76) |
|      |     | Yamada et al. 2001 (36) | Asian | 105 | 210 | No T allele was identified |
|      |     | Hsing et al. 2001 (49) | Asian | 268 | 495 | No T allele was identified |
|      |     | Soderstrom et al. 2002 (54) | European | 176 | 161 | AT vs AA 1.29 (0.40–4.15) |

| AR | (CAG)n | Kantoff et al. 1997 (57) | European | 590 | 802 | LL vs SS 0.47 (0.20–1.12) |
|    |       | Margiotti et al. 2000 (55) | European | 108 | 121 | LL vs SS 0.95 (0.51–1.72) |
|    |       | Latil et al. 2001 (37) | European | 226 | 156 | LL vs SS 0.50 (0.11–2.26) |
|    |       | Hsing et al. 2001 (49) | Asian | 268 | 495 | LL vs SS 0.74 (0.07–8.31) |

A shorter repeat was associated with younger age at diagnosis and higher grade and stage.
<table>
<thead>
<tr>
<th>Gene Polymorphism</th>
<th>Study (Reference)</th>
<th>Racial descent</th>
<th>Eligible subjects (no.)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prostate cancer</td>
<td>Controls</td>
</tr>
<tr>
<td>Hsing et al. 2000 (69)</td>
<td>Asian</td>
<td>190</td>
<td>304</td>
<td>&lt; 23 vs 23</td>
</tr>
<tr>
<td>Lange et al. 2000 (79)</td>
<td>European</td>
<td>133</td>
<td>305</td>
<td>21 vs &gt; 21</td>
</tr>
<tr>
<td>Latil et al. 2001 (37)</td>
<td>European</td>
<td>226</td>
<td>158</td>
<td>20 vs &gt; 24</td>
</tr>
<tr>
<td>Beilin et al. 2001 (76)</td>
<td>European</td>
<td>545</td>
<td>456</td>
<td>Every 5 repeats</td>
</tr>
<tr>
<td>Panz et al. 2001 (64)</td>
<td>European, African</td>
<td>40</td>
<td>40</td>
<td>Cases had a shorter repeat length than controls</td>
</tr>
<tr>
<td>Modugno et al. 2001 (65)</td>
<td>European</td>
<td>449</td>
<td>558</td>
<td>&lt; 23 vs 23</td>
</tr>
<tr>
<td>Balic et al. 2002 (62)</td>
<td>European</td>
<td>82</td>
<td>145</td>
<td>18 vs &gt; 18</td>
</tr>
<tr>
<td>Mononen et al. 2002 (63)</td>
<td>European</td>
<td>461</td>
<td>574</td>
<td>18 vs &gt; 18</td>
</tr>
<tr>
<td>Chen et al. 2002 (71)</td>
<td>European</td>
<td>300</td>
<td>300</td>
<td>&lt; 22 vs 22</td>
</tr>
<tr>
<td>Chang et al. 2002 (72)</td>
<td>European, African</td>
<td>245</td>
<td>211</td>
<td>21 vs 22</td>
</tr>
<tr>
<td>Gsur et al. 2002 (75)</td>
<td>European</td>
<td>190</td>
<td>190</td>
<td>23 vs 20</td>
</tr>
<tr>
<td>(GGN)n Irvine et al. 1995 (70)</td>
<td>European, Asian, African</td>
<td>68</td>
<td>123</td>
<td>Non-16 vs 16</td>
</tr>
<tr>
<td>Stanford et al. 1997 (68)</td>
<td>European</td>
<td>301</td>
<td>277</td>
<td>16 vs &gt; 16</td>
</tr>
<tr>
<td>Platz et al. 1998 (80)</td>
<td>European</td>
<td>582</td>
<td>794</td>
<td>23 vs Non-23</td>
</tr>
<tr>
<td>Edwards et al. 1999 (73)</td>
<td>European</td>
<td>178</td>
<td>195</td>
<td>16 vs &gt; 16</td>
</tr>
<tr>
<td>Correa-Cerro et al. 1999 (74)</td>
<td>European</td>
<td>132</td>
<td>105</td>
<td>Every 1 repeat</td>
</tr>
<tr>
<td>Hsing et al. 2000 (69)</td>
<td>Asian</td>
<td>190</td>
<td>304</td>
<td>16 vs &gt; 16</td>
</tr>
<tr>
<td>Chen et al. 2002 (71)</td>
<td>European</td>
<td>300</td>
<td>300</td>
<td>17 vs &gt; 17</td>
</tr>
<tr>
<td>Chang et al. 2002 (72)</td>
<td>European, African</td>
<td>245</td>
<td>211</td>
<td>16 vs 17</td>
</tr>
<tr>
<td>(CAG)n Platz et al. 2000 (85)</td>
<td>European</td>
<td>581</td>
<td>786</td>
<td>28/28 vs 28/29</td>
</tr>
<tr>
<td>Hsing et al. 2002 (84)</td>
<td>Asian</td>
<td>189</td>
<td>299</td>
<td>28/28 vs 29/29</td>
</tr>
<tr>
<td>(TTTA)n Latil et al. 2001 (37)</td>
<td>European</td>
<td>226</td>
<td>156</td>
<td>187 bp vs 167 bp</td>
</tr>
<tr>
<td>Arg264Cys Modugno et al. 2001 (65)</td>
<td>European</td>
<td>88</td>
<td>241</td>
<td>CT vs CC</td>
</tr>
</tbody>
</table>

Cl: confidence interval; OR: odds ratio.
A1, allele 1; A2, allele 2; L, leucine; V, valine; A, alanine; T, threonine; L, long allele [(TA)9 and (TA)18]; S, short allele [(TA)0]; R, arginine; Q, glutamine; C, arginine; T, cysteine.
The numbers of the contrast column refer to microsatellite repeats.
prostate cancer and have produced inconsistent results (Table 1). Shorter alleles of the CAG repeat seem to be associated with a modest increase in prostate cancer risk (62–70). Other studies, however, reported no association, or a weak and not statistically significant association, between shorter CAG repeat alleles and prostate cancer (37, 71–79). Interestingly, the frequency distribution of the AR gene CAG repeat length varies among different racial/ethnic groups. Shorter alleles are found more frequently in African–American men who have a higher incidence of prostate cancer. Conversely, populations at lower risk of prostate cancer (Caucasians and Asians) exhibit a relatively high number of CAG repeats (70, 81). The role of the GGN trinucleotide repeat in prostate cancer predisposition is also controversial (68–74, 80).

Two additional AR gene polymorphisms have been investigated for their association with prostate cancer: the R726L (a substitution of leucine for arginine at codon 726) in exon 5 and the G1733A single nucleotide polymorphism, designated the S1 and S2 alleles, respectively of a diagnostic cleavage site for the Stu I restriction endonuclease. The R726L polymorphism, which alters the transactivation specificity of the AR protein, has been associated with an almost sixfold increased prostate cancer risk in Finnish men (82). The S1 Stu I allele was shown to be associated with a threefold higher prostate cancer risk among African–American men under the age of 65 years (83).

**AR coactivators**

The AIB1 gene has two distinct CAG trinucleotide repeats. Two studies have investigated the role of AIB1 in prostate cancer: one found a positive association between AIB1 CAG repeat length and prostate cancer (84), and the other reported no association (85) (Table 1). Future studies are needed to investigate the effect of AR coactivators in prostate cancer risk.

**HSD3B2**

Inactivation of DHT in the prostate is an important determinant of intracellular DHT concentration and a potential modulator of androgenic activity in the prostate gland. Incomplete inactivation or slower degradation of DHT within the prostate can lead to the accumulation of DHT and, perhaps, increased androgenic action. Thus, enzymes that inactivate DHT may play a role in predisposition to prostate cancer. HSD3B2 is located on chromosome 1 (1p13.1) and encodes the 3β-hydroxysteroid dehydrogenase type 2 enzyme that initiates the irreversible inactivation of DHT within the prostate. A complex dinucleotide repeat polymorphism has been reported in the third intron of the HSD3B2 gene (86). Devgan et al. (87) examined the distribution of the (TG)n(TA)n(CA)n repeat in the HSD3B2 gene in high-risk African descent subjects, intermediate-risk European descent subjects, and low-risk Asian descent subjects. A total of 25 different alleles were identified, of which the 289 bp allele was the most common allele in all population groups. Interestingly, a 275 bp allele was significantly more common among African–American men, a 340 bp allele among European–American men and a 281 bp allele and alleles ranging from 302 to 334 bp were found to be significantly more common among Asian men. However, functional effects of the different alleles have not yet been reported and no studies have elucidated prostate cancer risk associated with a particular allele.

**CYP19**

The CYP19 gene is located on chromosome 15 (15q21.1) and encodes the enzyme aromatase that catalyzes the irreversible conversion of androstenedione to estrone and testosterone to estradiol. Aromatase is present in the gonads and in the extragonadal tissue, including the prostate and adipose tissue. Aromatase mRNA and protein have both been detected in benign prostatic hyperplasia (BPH) and prostate cancer tissue (88, 89). Two studies have investigated the role of CYP19 in prostate cancer (37, 65) (Table 1). One study found a positive association with the tetranucleotide repeat (TTTA)n in intron 4 of the CYP19 gene (37), and the other reported that Arg264Cys polymorphism (a C to T substitution in exon 7) was associated with a non-significant increase in the risk of prostate cancer (65).

**Conclusions**

Despite the evidence linking androgens and prostate cancer, molecular epidemiological studies have yielded conflicting results. Postulated genetic associations for prostate cancer need to be carefully validated across several studies, since early and small genetic association studies may come up with spurious findings (90). A very large number of subjects is needed to establish or refute a genetic association of modest magnitude and even larger numbers are needed to validate subgroup differences, let alone more subtle associations such as gene–gene and gene–environment interactions. Furthermore, genetic associations for such a multigenetic disease are likely to have relatively small odds ratios requiring large sample sizes to clarify the association.

Some other limitations of genetic association studies should be acknowledged. First, prostate cancer is very common and thus some non-differential misclassification bias is possible. The majority of the considered studies could not exclude latent prostate cancer cases in the control group and some young control subjects...
may have developed prostate cancer during the subsequent years. The choice of an appropriate age window for assessing a postulated genetic risk factor for prostate cancer is difficult. Studies of younger subjects may be more suitable for identifying risk factors that result in early carcinogenesis. Conversely, selection of younger subjects may be less appropriate if hormonal or other influences regulated by the postulated risk factor are more important in later ages. Second, control groups included a large, often unknown proportion of subjects with BPH. BPH may also be androgen dependent and affected by these same polymorphisms. Third, genetic association studies can suffer from publication bias; null studies are much less likely to be submitted or to be accepted for publication.

Most current genetic association studies investigate common polymorphisms in specific genes without considering the functional consequences of these polymorphisms, making the results of such studies difficult to interpret (2, 3). For example, a particular association between a specific genetic marker and prostate cancer risk may be significant by chance or due to multiple comparisons. Furthermore, a postulated association may merely reflect linkage disequilibrium of the genetic polymorphism to another truly causative marker (2, 3).

Finally, the prevalence of prostate cancer in the population probably results from complex interactions among many genetic and environmental factors. Cumulative lifetime exposure to androgens, as well as environmental exposures, could play an important role in the development of prostate cancer in genetically predisposed men. It is likely that a set of genetic polymorphisms rather than a single polymorphism can alter hormone levels and prostate cancer risk. The development of a polygenic model for prostate cancer incorporating multiple loci from the individual genes may yield better preventive, diagnostic, and therapeutic strategies.

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