Comprehensive Assessment of Candidate Genes and Serological Markers for the Detection of Prostate Cancer

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Abstract

We examined whether selected polymorphisms in 11 candidate genes and serum levels of insulin-like growth factor 1 (IGF-I) help predict the presence of prostate cancer among patients prescreened with prostate-specific antigen (PSA) and digital rectal exam (DRE). We studied 1031 consecutive men who underwent one or more prostate biopsies because of an elevated PSA level (>4 ng/ml) or an abnormal DRE. Eleven candidate genes were examined, including the androgen receptor, SRD5A2, CYP17, CYP3A4, vitamin D receptor, PSA, GST-T1, GST-M1, GST-P1, IGF-I, and IGF binding protein 3. We also measured serum IGF-I levels before biopsy. Of the 1031 men, 483 had cancer on any biopsy (cases) and 548 men had no cancer (controls). Age, ethnicity, total PSA, and DRE result were strongly predictive of the presence of prostate cancer. The mean IGF-I level for cases (119.4 ng/ml) was lower than for controls (124.4 ng/ml, P = 0.05) and were not predictive for the presence of prostate cancer. We found no associations between the androgen receptor, SRD5A2, CYP17, CYP3A4, vitamin D receptor, GST-M1, GST-P1, and IGF binding protein 3 genotypes and prostate cancer risk. The adjusted odds ratios for having prostate cancer for patients with the GST-T1 and IGF-I variant alleles were 1.64 (95% confidence interval, 1.1–2.4; P = 0.01) and 1.70 (95% confidence interval, 1.1–2.7; P = 0.02), respectively. Nine of 11 candidate genes were not significantly predictive for prostate cancer in a clinical setting. The GST-T1 and IGF-I polymorphisms demonstrated modest associations with prostate cancer risk. IGF-I levels were not helpful in identifying patients with prostate cancer at the time of biopsy.

Introduction

Prostate cancer is the most common malignancy diagnosed in males and is a major public health problem (1, 2). The most frequent screening test used to help to identify patients with prostate cancer is the measurement of serological levels of serum prostate-specific antigen (PSA; Ref. 3). Two large clinical trials are under way to establish whether prostate cancer screening reduces mortality (4, 5).

The sensitivity of PSA as a screening test is high (6), but the positive predictive is relatively low for screening of the general population (7). Many benign conditions of the prostate gland, including benign prostatic hyperplasia and prostatitis, which are prevalent among older men, also elevate PSA levels (8), and consequently, many men are unnecessarily subjected to invasive prostatic biopsies. The use of variations of the PSA test, including PSA density, and the free:total PSA ratio have not eliminated this problem (9).

Association studies have examined the significance of several candidate genes based on biological pathways associated with prostate carcinogenesis. A significant number of these genes encode for proteins involved in androgen metabolism (10). Polymorphic alleles of the androgen receptor (11, 12), the vitamin D receptor (13), 5-α reductase (14, 15), CYP17 (16), and CYP3A4 (17) genes have been associated with the presence of prostate cancer in some studies.

The CAG repeat polymorphism of the X-linked androgen receptor gene has been well described (18). The average length of the CAG repeat in the population is reported to be 21 repeat units, with a range of 11–31 in healthy individuals (18). Men with a CAG repeat sequence of 19–22 units have a relative risk of 1.5–2.1 for developing prostate cancer, compared with patients with a longer CAG repeat (11, 12). We described an increased rate of prostate cancer progression for men with CAG repeats of ≤18 units (19).

A substitution of valine (V) to leucine (L) in codon 89 in exon 1 of the 5-α reductase enzyme gene (SRD5A2) has been associated with different levels of 5-α reductase-2 activity and with prostate cancer risk (14, 15). Levels of 5-α reductase-2 expression are higher in human prostate cancer cells than in benign prostatic cells (20). It is believed that polymorphic variants with the SRD5A2 gene influence 5-α reductase-2 activity (14). A polymorphism of the SRD5A2 gene, consisting of a valine (V) to leucine (L) substitution at codon 89 in exon 1 is associated with different levels of 5-α reductase-2 activity and with prostate cancer risk (14, 21). We reported that patients with the V allele have a 2.5 fold increase in risk for prostate cancer compared with men with the L allele (15).

Two genes encoding for the cytochrome p-450 enzymes, CYP17 and CYP3A4, influence the rate of androgen metabolism. The CYP17 enzyme is the rate-limiting step in androgen biosynthesis from 17-α hydroxylase and 17,20-lyase (16). The A2 allele of the CYP17 gene represents a thymine to cytosine substitution and has been associated with a 1.2- to a 2.8-fold...
increase in the risk of prostate cancer (22, 23). The CYP3A4
gene metabolizes testosterone to less active metabolites (17). A
germ-line genetic variant in the 5′ regulatory region of the
CYP3A4 gene that substitutes an alanine for a glycine at codon
293 has been associated with a 1.7–9.5-fold increase in risk for
prostate cancer (17, 24).

There have been many polymorphisms described in the
vitamin D receptor gene (25) and several have been linked to
prostate cancer risk (13). There are many hypotheses linking
the role of vitamin D, its receptor, and prostate carcinogenesis,
including different UV radiation and prostate cancer risk (26)
and in vitro expression of the vitamin D receptor in prostate
cancer cells (27).

Other candidate genes which have been linked to prostate
cancer include the PSA gene and glutathione S-transferase
(GST) enzyme genes. A G/A polymorphism of the androgen
receptor domain of the PSA gene has been reported to be
positively associated with prostate cancer risk (28). Xue et al.
(28) found that this polymorphism was also associated with
serum PSA levels and with prostate cancer stage at presenta-
tion. Two subsequent studies yielded conflicting results. Xu et al.
(29) found no relationship with this polymorphism and
prostate cancer risk. In contrast, another group found a positive
association (odds ratio 2.9 for prostate cancer for patients with
the A-allele) with this gene (30).

The GST group of enzymes (GSTs, type M/T/P) conjugate
glutathione intermediate metabolites that can be carcinogenic
(31, 32). Homozygous deletions result in absent GST enzymes,
which results in poorer elimination of carcinogens, possibly
increasing the risk for carcinogenesis (31). Certain deletions of
the GST family of genes have been associated with increased
risk of cancer of several sites known to be strongly related to
carcinogens, including lung (33), colon (34), and breast (35).
However, patients with one or more nondeleted GST-T1 alleles
were reported to have a 2-fold increase in prostate cancer (36).

High serum levels of insulin-like growth factor type I
(IGF-I) and low serum levels of IGF binding protein type-3
(IGFBP-3) have been shown to be associated with an increased
risk of prostate cancer (37, 38). Polymorphisms of the IGF-I
and IGFBP-3 genes have been shown to be associated with
serum IGF-I and IGFBP-3 levels (39, 40), but these variants have
not been examined for prostate cancer risk. A micro-
satellite polymorphism (variable length CA repeat sequence)
has been identified in the promoter region of the IGF-I gene
(41). The most common allele has 19 CA-repeats (CA19) and
that those with the homozygous CA19/CA19 genotype have
been found to have lower serum IGF-I levels (41). A single bp
polymorphism in the promoter region of the IGFBP-3 gene has
been described and has been shown to be associated with serum
IGFBP-3 levels (39). Those with the C-allele had lower
IGFBP-3 levels (39). These polymorphisms of the IGF-I and
IGFBP-3 genes could be associated with prostate cancer, given
the strong relationships found between their serum levels and
prostate cancer risk.

The clinical significance of these biomarkers has not been
established. To date, no studies have examined the use of these
markers to identify patients at increased risk for having prostate
cancer. Previous association studies have been based on highly
selected controls who have a low inherent risk for prostate
cancer, namely with a low PSA and a normal digital rectal
examination (DRE) or patients with histological evidence of only benign
prostatic hyperplasia. Additional case-control studies of this
design are not needed. However, these biomarkers have not
been tested in a true clinical setting where a patient requires a
prostate biopsy because of an abnormal screening test result
with PSA and DRE. It would be important to evaluate the risk
for prostate cancer based on these biomarkers among uns-
elected controls beyond the low predictive ability of current
screening tests of PSA and DRE.

To establish whether these genetic markers are predictive
for prostate cancer, we genotyped the androgen receptors
SRD5A2, CYP17, CYP3A4, vitamin D receptor, PSA, GST-M/
M/P1I, IGF-I, and IGFBP-3 polymorphisms among 1031 men
who underwent a prostate biopsy because of a PSA of ≥4.0
ng/ml or an abnormal DRE. We also measured serum-free PSA,
IGF-I, and IGFBP-3 levels before prostate biopsy.

Materials and Methods

Study Subjects. Patients were drawn from a consecutive sample
of 1103 eligible men who were referred to the Prostate
Center of the University Health Network, between June 1998
and June 2000, because of either a PSA value ≥4.0 ng/ml or
because of an abnormal DRE. In Ontario, there are no formal
criteria for PSA screening, but the practice is widespread. The
study population was not part of a formal screening program,
but it is representative of all clinical referrals to the Prostate
Center. No patient had a history of prostate cancer before
prostate biopsy, and no patients were included who were re-
ferred for tertiary management.

Of the 1103 patients, 1031 (93.4%) consented to partici-
pate in the study. Blood samples were collected before clinical
prostate examination. Plasma was separated from blood sam-
ple and was stored at −70° C. A urological history, which
included the American Urological Association Symptom Score
describing the severity of lower urinary tract voiding symp-
toms, was obtained (42). The results of DRE, performed by one
evaluator (A. T.) were recorded. Systematic ultrasound-guided
needle biopsies that obtain 6–12 samples were performed,
using an 18-gauge spring loaded biopsy device (Bard Magnum,
Murray Hill, NJ). The primary end point was the histological
presence of adenocarcinoma of the prostate in the biopsy spec-
imen. Grade was evaluated by the Gleason scoring system (43).
All research was conducted with informed consent and with
the approval of the hospital research ethics board.

Of the patients who did not have evidence of cancer on the
initial prostate biopsy, repeat prostate biopsies were offered
because cancer can be detected in 15–30% of patients in
subsequent biopsies who have an initial negative prostate bi-
opsy (44, 45). Of the 1031 patients, 639 patients underwent one
biopsy session, of whom 347 (54.3%) had cancer. Of the
remaining 392 men, 328 had two prostate biopsy sessions with
128 (39.0%) men having cancer on the second biopsy, and 63
men had three or more biopsy sessions with 8 (12.5%) having
cancer on the third biopsy. In total, of the 1031 patients, 483
(46.9%) had cancer (cases) and 548 (53.1%) had no evidence
of cancer (controls).

Genetic Analysis. DNA samples from each patients were ex-
tracted from peripheral blood leukocytes using standard pro-
tocols. Eleven polymorphisms were examined, including the
androgen receptor, SRD5A2, CYP17, CYP3A4, vitamin D re-
ceptor, PSA, GST-M/P1I, IGF-I, and IGFBP-3 genes
(Table 1). To ensure for quality control of the restriction di-
gests, we randomly duplicated 25% of samples for comparison
for each polymorphism. All gel readers were blinded to the
primary end point and covariates.

Serological Analysis. Both free and total PSA levels were
measured using commercially available kits, performed on the
Immulite chemiluminescence immunoassay system (Diagnostic
Products Corporation, San Diego, CA) according to the man-
manufacturer’s recommendations. Plasma levels of IGF-I and IGFBP-3 were determined using assay kits based on ELISA with reagents from Diagnostic Systems Laboratory (Webster, TX; Ref. 37).

**Data Analysis.** We compared the frequencies of the candidate polymorphic variants and the levels of IGF-I and IGFBP-3 between prostate cancer cases and controls. The effect of the polymorphic alleles in predicting prostate cancer was examined using univariate and multivariate logistic regression modeling, controlling for age, serum PSA level, DRE, ethnic background, using univariate and multivariate logistic regression modeling, and the presence of lower urinary tract voiding symptoms.

The SRD5A2, CYP17, CYP3A4, vitamin D receptor, PSA, GST-T1, and IGFBP-3 genes were dichotomized into either homozygous deletions (0) or at least one nondeleted allele (1), according to Rebbeck et al. (36), who showed a positive association between the nondeleted genotype of the GST-T1 gene and prostate cancer risk. The IGF-I gene was categorized into two 19CA alleles, one 19CA allele, or no 19CA allele (40).

Total serum PSA level was categorized into four groups: (a) ≤4.0; (b) 4.1–10.0; (c) 10.1–20.0; and (d) >20.0 ng/ml. Free-total-PSA was divided into quartiles of the controls grouped in descending order because low free:total PSA ratios are associated with a higher risk for prostate cancer (46). IGF-I and IGFBP-3 levels were categorized into their quartile distribution of the control group. DRE was categorized into three groups: (a) nonpalpable; (b) palpable asymmetric firmness; and (c) palpable nodule. Lower urinary tract symptoms were dichotomized as present or absent. Ethnicity was categorized into four groups: (a) Caucasian; (b) black; (c) Asian; and (d) other.

**Results**

The mean age at biopsy of the 1031 men was 65.4 years (range, 41.7–90.8 years). The mean PSA level was 12.3 ng/ml (range, 0.4–498.8 ng/ml), whereas 56.5% had a normal DRE. The majority of the patients were Caucasian (865, 83.9%); 90 (8.7%) and 59 (5.7%) were black and Asian, respectively. Twelve percent of patients had at least one relative with prostate cancer.

Of the 1031 men, 483 men (46.9%) were found to have adenocarcinoma of the prostate at biopsy (cases). Of the 548 men with no evidence of invasive cancer (controls), 292 (53.3%) had one prostate biopsy, 200 (36.5%) men had two prostate biopsies, and 56 (10.2%) had three or more prostate biopsies. Of these control patients, 39 had normal prostate tissue, 406 had inflammation/benign prostatic hyperplasia, and 103 had prostatic intraepithelial neoplasia.

The mean age of the cases (66.6 years) was higher than that of the controls (64.4 years, P = 0.0001). Cases were more

### Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Method</th>
<th>Upstream</th>
<th>Downstream</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen receptor</td>
<td>CAG repeat</td>
<td>Direct sequencing</td>
<td>GTGGAAGATTCACCCAAGCCT</td>
<td>TCGGTCTTCCTCATCCAGGA</td>
<td>19</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>V89L</td>
<td>RFLP</td>
<td>CCGCTGGTCTCTGCAGGAGCT</td>
<td>GTGAAAGCGGCGGCTGCGTG</td>
<td>15</td>
</tr>
<tr>
<td>CYP17</td>
<td>Single nucleotide base change T/C</td>
<td>RFLP</td>
<td>CATTGCACACTTGAGGTC</td>
<td>GGCTCTGGGTTACCTG</td>
<td>23</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>NFSE</td>
<td>CSGE</td>
<td>AACAGGGGCTGGAACACCA</td>
<td>TTCTCTGGCCGTGCA</td>
<td>17</td>
</tr>
<tr>
<td>Vitamin D receptor</td>
<td>Rsnd (intron 8)</td>
<td>RFLP</td>
<td>CAACCAAGACTCAAGATGCTACGCCTGCA</td>
<td>AACCAGGCGGAAAGGTCGAGG</td>
<td>25</td>
</tr>
<tr>
<td>PSA</td>
<td>Single bp change G/A</td>
<td>RFLP</td>
<td>TTGTATGAGAATGCAGGAGGAGTCTG</td>
<td>TCCCCCAAGAGCTAATTTA</td>
<td>28</td>
</tr>
<tr>
<td>GST-T1</td>
<td>Homozygous deletion</td>
<td>RFLP</td>
<td>TTTCTCTACTGTGCTCACCTGCT</td>
<td>TCAGCCGATCTGCGGCA</td>
<td>36</td>
</tr>
<tr>
<td>GST-M1</td>
<td>Homozygous deletion</td>
<td>RFLP</td>
<td>CTGCTCTCTCTTAGTGGTGG</td>
<td>CTGATTTGAGCAGCATGC</td>
<td>36</td>
</tr>
<tr>
<td>GST-P1</td>
<td>Single bp change I/V</td>
<td>RFLP</td>
<td>CAACTCTTACCACGGTCAC</td>
<td>GAAGAGCAAGGACAGTT</td>
<td>32</td>
</tr>
<tr>
<td>IGF-1</td>
<td>19-repeat allele</td>
<td>VNTR</td>
<td>GCTAGCCAGTGGTGTATTT</td>
<td>ACCACCTCGGAGAAGGTA</td>
<td>39</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>Single bp change A/C</td>
<td>RFLP</td>
<td>CCACAGGTACACAGGAATG</td>
<td>AGGCCGAGTCTGCGATCG</td>
<td>39</td>
</tr>
</tbody>
</table>

*NFSE, nifedipine specific element; CSGE, conformation-sensitive gel electrophoresis; VNTR, variable number of tandem repeats.

### Table 2

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of cases (n = 483)</th>
<th>Number of controls (n = 548)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>10 (2.1%)</td>
<td>22 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>51–60</td>
<td>106 (21.9%)</td>
<td>136 (24.8%)</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>195 (40.4%)</td>
<td>267 (48.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>172 (35.5%)</td>
<td>122 (22.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.0</td>
<td>18 (3.7%)</td>
<td>76 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>4.1–10.0</td>
<td>261 (54.1%)</td>
<td>303 (55.3%)</td>
<td></td>
</tr>
<tr>
<td>10.1–20.0</td>
<td>143 (29.6%)</td>
<td>139 (25.4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>61 (12.6%)</td>
<td>30 (5.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Digital rectal exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpalpable</td>
<td>238 (49.3%)</td>
<td>343 (62.6%)</td>
<td></td>
</tr>
<tr>
<td>Asymmetry</td>
<td>115 (23.8%)</td>
<td>116 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>130 (26.9%)</td>
<td>89 (16.2%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>421 (87.2%)</td>
<td>444 (81.0%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>45 (9.3%)</td>
<td>45 (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>12 (2.5%)</td>
<td>47 (8.6%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.0%)</td>
<td>12 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>417 (86.3%)</td>
<td>487 (88.9%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>66 (13.7%)</td>
<td>61 (11.1%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Obstructive urinary symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>112 (23.2%)</td>
<td>107 (19.5%)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>371 (76.8%)</td>
<td>441 (80.5%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>
likely to have had an abnormal DRE and, on average, had a higher PSA level than controls (Table 2). Asians had a lower rate of prostate cancer than Caucasians or blacks (Table 2).

To determine whether the genotypes of each candidate gene predicted the presence of cancer, we used two control groups. The first control group consisted of all patients with no evidence of cancer on any prostate biopsy. The second group consisted only of patients who had at least two prostate biopsy sessions that did not reveal any malignancy.

Two genes, the GST-T1 and IGF-I polymorphisms, were found to be associated with an increased probability for prostate cancer detection. Other genes did not show any significant effects in altering the risk for prostate cancer (Table 3). Using the first control group, the adjusted odds ratio for prostate cancer for patients with the nondeleted allele of the GST-T1 gene was 1.34 ($P = 0.09$), compared with patients with homozygous deletions (Table 4). Using the second control group (men with at least two negative biopsies), the odds ratio for prostate cancer based on the GST-T1 variant allele was 1.64 (95% confidence interval (CI), 1.1–2.4; $P = 0.01$). Because the adjusted odds ratios for the IGF-I polymorphism were similar for patients with one and with two of the 19 alleles (Table 4), we combined the two groups. The adjusted odds ratios for having prostate cancer for patients with at least one IGF-1 19-repeat allele was 1.36 (95% CI, 0.9–2.0; $P = 0.12$). Using the second control group, the adjusted odds ratios for the IGF-I polymorphism achieved marginally significance (odds ratio = 1.70, 95% CI, 1.1–2.7; $P = 0.02$).

When we compared the genotypes with the established risk factors, there were no significant differences in the genotype distributions by age, PSA, DRE, histological grade, and number of needle biopsies performed. We stratified patients into the following: ≤65 or >65 years; ≤10 or >10 ng/ml PSA; normal or abnormal DRE; low, moderate, or high grade; and ≤8 or >8 needle cores. The adjusted odds ratios for prostate cancer for each of those subgroups did not significantly change from the multivariate analysis. However, there were significant differences in the distribution of the genotypes by ethnicity.
Table 4  Univariate and multivariate analysis of all covariates for prostate cancer risk, including established risk factors, 11 candidate genes, and IGF-1/IGFBP-3 levels

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Crude odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (continuous, per year)</td>
<td>1.04</td>
<td>1.0–1.1</td>
<td>0.0001</td>
<td>1.04</td>
<td>1.0–1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>PSA level (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10.0</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1–20.0</td>
<td>1.40</td>
<td>1.1–1.8</td>
<td>0.01</td>
<td>1.15</td>
<td>0.8–1.6</td>
<td>0.37</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>2.76</td>
<td>1.7–4.4</td>
<td>0.0001</td>
<td>1.78</td>
<td>1.1–3.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Free:Total PSA ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.17</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.12–0.17</td>
<td>2.14</td>
<td>1.4–3.4</td>
<td>0.001</td>
<td>2.40</td>
<td>1.5–3.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>0.07–0.11</td>
<td>3.92</td>
<td>2.6–6.0</td>
<td>0.0001</td>
<td>4.83</td>
<td>3.1–7.6</td>
<td>0.0001</td>
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<tr>
<td>&lt;0.07</td>
<td>5.56</td>
<td>3.7–8.5</td>
<td>0.0001</td>
<td>6.68</td>
<td>4.2–10.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Digital rectal exam</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Assymetry</td>
<td>1.43</td>
<td>1.1–1.9</td>
<td>0.02</td>
<td>1.65</td>
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Candidate Genes and Prostate Cancer Risk

(1434)

Table 4 Continued

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<td>1.27</td>
<td>0.9–1.2</td>
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*Each genetic marker assumed to be independent. Thus, each genetic marker adjusted for age, PSA, free-total prostate-specific antigen (PSA) ratio, digital rectal exam (DRE), ethnicity, family history and obstructive voiding symptoms. IGF-I and IGFBP-3 considered together in a multivariate model adjusting for age, PSA, free-total PSA ratio, DRE, ethnicity, family history and obstructive voiding symptoms.

b CAG repeat units also considered as continuous variable. Adjusted odds ratio = 1.01 for prostate cancer per CAG repeat unit increase (95% confidence interval, 0.97–1.05; P = 0.57).

To control for possible confounding by ethnicity, we determined the probability for prostate cancer by each genotype within each ethnic group. No significant differences were found.

Finally, we examined whether serum IGF-I and IGFBP-3 levels predicted the presence of prostate cancer and whether the levels of these proteins correlated with their genotypes. The mean IGF-I levels were slightly lower for cases (119.4 ng/ml) than for controls (124.4 ng/ml, P = 0.05). The mean IGFBP-3 levels were also lower among the cases (2277.7 ng/ml) than the controls (2306.3 ng/ml, P = 0.02). The adjusted odds ratio for detecting prostate cancer for patients with the highest quartile of IGF-I levels was 0.7 (95% CI, 0.5–0.9), compared with patients with lowest quartile level (Table 5). We found no correlation between serum IGF-I levels and the IGF-I polymorphism (P = 0.69). However, there was a strong correlation between serum IGFBP-3 levels and the IGFBP-3 polymorphism. The mean IGFBP-3 levels for the AA, AC, and CC genotypes were 2361.2, 2277.9, and 2174.3 ng/ml, respectively (P = 0.0002). IGF-I and IGFBP-3 levels were positively correlated with each other (r = 0.64, 0.0001) and were negatively correlated with age (r = −0.25 for IGF-I, P = 0.0001; r = 0.26 for IGFBP-3, P = 0.0001). Neither level correlated with PSA level at biopsy (r = 0.03 for IGF-I, P = 0.35; r = 0.05 for IGFBP-3, P = 0.09).

Discussion

We studied associations between selected polymorphisms of 11 candidate prostate cancer genes and the probability for prostate cancer among an unscreened population of men prescreened with PSA and DRE. Among these genes, only the GST-T1 and IGF-I polymorphisms were associated with a higher risk for having prostate cancer (adjusted odds ratios 1.64 and 1.70 for the variant alleles, respectively).

There have been numerous studies examining the association between specific polymorphisms of candidate genes and prostate cancer. However, these studies have mainly been case-control or nested-case control study designs with selected controls (11–17, 22–24, 26, 28–32, 36). In our study, our controls were derived from a group prescreened with PSA and a DRE. For these patients, there could be a clear clinical application in predicting prostate cancer by these markers. Ours is the first study to apply these polymorphisms to predict the presence of prostate cancer in a screening setting. Given the high frequency of the variant alleles of each of the polymorphisms, it is possible that these could be used as adjuncts to current prostate cancer screening tests. We chose 11 polymorphisms from selected candidate genes most frequently reported to be associated with increased prostate cancer risk. Marginal positive findings were found for the GST-T1 and IGF-I polymorphisms.

This was found with the second control group who underwent at least two or more negative prostate biopsies. This was done to reduce misclassification of cases and controls. It has been well established that patients who undergo one prostate biopsy may have a 15–30% chance of having cancer after a second prostate biopsy is performed (44, 45, 47–50). After having two negative prostate biopsies, the chances of having a malignancy is <5% (44, 45). However, 360 patients who had an initial negative biopsy did not undergo a repeat exam. The reasons for this included patient refusal, referring physician’s refusal, and loss to follow-up. After excluding these patients, the odds ratio estimates did not significantly change from the initial control group. Further study will be required in these genes to establish whether they will be of clinical importance but may be important in determining which patients will require a repeat biopsy after a negative biopsy.

On the other hand, despite using a control group who had repeat biopsies that demonstrated no evidence of cancer, the potential for misclassifying patients as controls is an important limitation to recognize in this study. The ideal control group would be men with normal PSA and DRE results who have no histological evidence of cancer, which is beyond the scope of this study and would require a large prospective study with long follow-up to assess for prostate cancer development. However, in our study, our objective was to determine whether these genetic and serological factors would be an important adjunct to enhance the ability to detect prostate cancer in a cross-sectional, clinical setting. Past association studies with more rigid selection of controls have examined their relationship with prostate cancer. This study has shown that regardless of the association with prostate cancer, these factors may not be clinically important in detecting prostate cancer. Finding clinically significant results for these types of markers is possible. We have recently shown that a polymorphism of the human kallikrein-2 gene was an important predictor for prostate cancer in a similar study.
design (51). Nevertheless, it is important to acknowledge that this bias of misclassifying controls would tend to dilute case-control differences that could miss modest effects.

For a large number of the polymorphisms, there were significant differences in the allelic frequencies between ethnicities. However, when restricted to Caucasian subjects, no significant associations were found. Among these, the SRD5A2 polymorphism and prostate cancer risk has already been negatively affected by the presence of prostate cancer (52). Male mutant mice with no IGF-I activity showed lowered sex drive and are infertile and a significant reduction in the mass of prostate gland and in testosterone levels (53).

We found a modest correlation with the IGF-I polymorphism and prostate cancer risk (odds ratio, 1.70) (37). First demonstrated the ability of serum IGF-I levels to predict the probability of a future diagnosis of prostate cancer using the cohort from the Physicians’ Health Study. Men in the highest quartile of IGF-I levels had a relative risk of 4.3 for developing prostate cancer when compared with men in the lowest quartile. A follow-up study recently further showed that patients with IGF-I levels and low IGFBP-3 levels may be at increased risk for developing advanced stage prostate cancer (54). Because their original report, many other case-control and cohort studies have examined the relationship between IGF-I and prostate cancer showing both positive and negative associations, although all prospective studies have shown a positive association for the future development of prostate cancer (38, 55–57).

Among our patients, both IGF-I and IGFBP-3 levels were significantly lower among the cases compared with the controls. It is possible that IGF-I levels may be altered in the presence of prostate cancer in our study where levels were measured immediately before prostate biopsy. This is an important limitation of case-control studies. Chan et al. (37) in the Physicians’ Health Study had blood samples obtained ~8 years before the diagnosis of prostate cancer. This is consistent with the argument that a high IGF-I serum level is a risk factor for a future development of prostate cancer, rather than a tumor marker at diagnosis. In our study, IGF-I levels could have already been negatively affected by the presence of prostate cancer, given the case-control nature of the study.

We found a modest correlation with the IGF-I polymorphism and prostate cancer risk (odds ratio, 1.70). There was no correlation observed between the IGF-I levels and the IGF-I polymorphism. Allen et al. (40) also did not find a correlation between serum IGF-I levels and the CA repeat polymorphism among healthy middle-aged men. In contrast, we found a strong correlation with the IGFBP-3 polymorphism and serum IGFBP-3 levels but not with prostate cancer risk. Jernestrom et al. (39) reported a strong positive association with IGFBP-3 levels and its polymorphism among premenopausal females, which were in the same direction as our study.

In summary, none of the selected polymorphisms examined from the 11 candidate genes was identified to be a strong predictor of prostate cancer at biopsy and high serum IGF-I levels also was not predictive. Modest significant findings were found for the GST-T1 and IGF-I polymorphisms and further study will be required to examine their clinical significance for patients who require a prostate biopsy. Although strong correlations were found between the IGFBP-3 polymorphism and serum IGFBP-3 levels, their clinical significance among men at risk for prostate cancer is still unclear. Future studies will be required to evaluate other polymorphic variants of the same and new genes implicated to be associated with prostate cancer.

### Table 5

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<td>AG</td>
<td>375 (43.4%)</td>
<td>48 (48.9%)</td>
<td>18 (30.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>211 (24.4%)</td>
<td>14 (15.5%)</td>
<td>32 (52.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>VDR</td>
<td>Bb</td>
<td>221 (25.5%)</td>
<td>12 (13.3%)</td>
<td>5 (8.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Bb</td>
<td>317 (36.7%)</td>
<td>42 (46.7%)</td>
<td>11 (18.6%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GST-T1</td>
<td>0</td>
<td>164 (19.0%)</td>
<td>30 (33.3%)</td>
<td>18 (30.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>701 (81.0%)</td>
<td>60 (66.7%)</td>
<td>41 (69.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GST-M1</td>
<td>0</td>
<td>432 (49.9%)</td>
<td>25 (27.8%)</td>
<td>36 (61.0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>433 (50.1%)</td>
<td>65 (72.2%)</td>
<td>23 (39.0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GST-P1</td>
<td>LL/LL</td>
<td>439 (50.7%)</td>
<td>29 (32.2%)</td>
<td>35 (59.3%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>LN/LN</td>
<td>375 (43.4%)</td>
<td>52 (57.8%)</td>
<td>24 (40.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>51 (5.9%)</td>
<td>9 (10.0%)</td>
<td>0 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IGF-I</td>
<td>No 19 allele</td>
<td>106 (12.3%)</td>
<td>43 (47.8%)</td>
<td>16 (27.1%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>One 19 allele</td>
<td>407 (47.0%)</td>
<td>38 (42.2%)</td>
<td>32 (54.2%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Two 19 alleles</td>
<td>352 (40.7%)</td>
<td>9 (10.0%)</td>
<td>11 (18.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>AA</td>
<td>251 (29.0%)</td>
<td>15 (16.7%)</td>
<td>9 (15.3%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>433 (50.1%)</td>
<td>44 (48.9%)</td>
<td>24 (40.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>181 (20.9%)</td>
<td>31 (34.4%)</td>
<td>26 (44.0%)</td>
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</table>
androgen receptor gene and its relationship to prostate cancer. Proc. Natl. Acad. Sci. (Bethesda), PS:


Comprehensive Assessment of Candidate Genes and Serological Markers for the Detection of Prostate Cancer


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