Polymorphisms in estrogen bioactivation, detoxification and oxidative DNA base excision repair genes and prostate cancer risk

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To date, the potential impact of hormones on prostate cancer has predominantly focused on receptor-mediated events. However, catechol estrogens, if not inactivated by catechol-O-methyltransferase (COMT), can generate large quantities of reactive oxygen species (ROS). ROS may cause a spectrum of damage including oxidative DNA base lesions, which can lead to irreversible mutation(s) if they are not repaired by base excision repair (BER) systems. hOGG1 is a key enzyme in short patch BER because it recognizes and performs initial excision of the most common form of oxidative DNA base damage, 8-hydroxyguanine (8-oxo-dG). To investigate potential non-receptor-mediated estrogen effects, we evaluated the association between COMT Val158Met and hOGG1 Ser326Cys polymorphisms and prostate cancer in a family-based case–control study (439 prostate cancer cases, 479 brother controls). We observed no noteworthy associations between these polymorphisms and prostate cancer risk in the total study population. However, among men with more aggressive prostate cancer, the hOGG1 326 Cys/Cys genotype was inversely associated with disease (OR = 0.30; 95% CI = 0.09–0.98). Combining the lower activity CYP1B1 432 Leu/Leu or Leu/Val genotypes (which may decrease the level of catechol estrogens and ROS generated) with the hOGG1 326 Cys/Cys genotype and the XRCC1 399 Arg/Arg or Gln/Gln genotypes (which may enhance BER) resulted in an even further reduced risk in Caucasians with more aggressive disease (OR = 0.09; 95% CI = 0.01–0.56). Including the high-activity COMT 158Val allele to this combination also lowered aggressive prostate cancer risk but the effect was not as strong (OR = 0.20; 95% CI = 0.05–0.88). The decreased risk we observed with the hOGG1 326 Cys/Cys genotype confirms an earlier report and the further reduced risk found with the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys)-XRCC1 (Arg/Arg or Arg/Gln) genotype combination may lend new insights to the importance of ROS generated from non-receptor-mediated estrogenic mechanisms in more aggressive prostate cancer.

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer death among men in the United States (1). Although the etiology of this disease remains largely unknown, age, ethnicity, family history and steroid hormones appear to play a role (2,3). Polymorphisms in the androgenic pathway involving testosterone metabolism to dihydrotestosterone (DHT) have been well studied in prostate cancer (4–7) as these androgens are generally recognized as the most important hormones in adult males and DHT binding to the androgen receptor (AR) induces cellular proliferation in the prostate (8).

The role of estrogens in prostate cancer is less clear, and most of the research has focused on the estrogen receptor (9–11). However, non-receptor-mediated mutagenesis induced by oxidized estrogen metabolites may also contribute to prostate carcinogenesis. As shown in Figure 1, testosterone may be metabolized by CYP19 to O-estriol (E2), which has been shown to cause cancerous lesions in the prostate glands of Noble rats even at very low concentrations (12). The mechanism of E2 action probably involves its further metabolism to unstable catechol estrogens. CYP1B1 and CYP1A1 preferentially catalyze hydroxylation of E2 to form the catechol estrogens, 2- and 4-hydroxy-estriol (2-, 4-OH-E2), respectively (13). These catechol estrogens, if not inactivated by catechol-O-methyltransferase (COMT) (14), can generate large quantities of the superoxide anion (O2•−) and other reactive oxygen species (ROS) through futile redox cycling between catechol estrogens and E2-quinoine metabolites (15).

E2-quinones, if not conjugated by glutathione-S-transferase (GST) enzymes, could form DNA adducts that may lead to mutation (16). However, if ROS are not rapidly quenched by micronutrients or antioxidant enzymes, they may cause a spectrum of damage including oxidative DNA base lesions such as 8-hydroxyguanine (8-oxo-dG) (17). Prostate cells induced with increasing concentrations of catechol estrogens (4-OH-E2) were found to have increasingly higher levels of ROS and DNA damage (18). Compared with normal prostate tissue, higher levels of 8-oxo-dG have been observed in benign prostatic hyperplasia (BPH) (19) and a pro-oxidant state has been found in prostate cancer and the precursor, high-grade prostatic intraepithelial neoplasia (HGPIN) (20), 8-oxo-dG may then cause G:C to T:A (G→A) transversions in DNA (21), which are the most common mutations found in p53 (22) and ras (23).
DNA damage induced by ROS may be repaired by an elaborate network of enzymes. 8-oxo-dG and other single DNA base damage forms are preferentially repaired by the short patch pathway of the base excision repair (BER) enzyme system (24) (Figure 1). Human OGG1 (hOGG1) is a multi-functional DNA glycosylase that performs the initial step of recognizing the 8-oxo-dG damage and the subsequent step of hydrolyzing the N-glycosyl bond, which releases the damaged base but leaves a site of base loss [apurinic (AP) site] in the DNA (25). APE1 then recognizes and cleaves the AP site while XRCC1 provides the scaffolding for DNA polymerase β (Pol-β) and DNA ligase III (Lig3) to complete the repair process (26,27).

Although functional polymorphisms involved in estrogen bioactivation and detoxification have been implicated in other hormone-related cancers (28–31), their impact on prostate cancer has not been well studied. The CYP1A1 Ile462Val and the CYP1B1 Leu432Val polymorphisms have been associated with prostate cancer but most studies have been conducted in Japanese populations (32–36). We previously reported a weak association with the CYP1B1 432 Leu/Val genotype compared with the Leu/Leu genotype among men with less aggressive disease in a predominantly Caucasian sibling-based case–control study \( \text{OR} = 0.54; 95\% \text{ CI} = 0.28–1.05; P = 0.07 \) (7).

The \((\text{TTTA})_7\) and \((\text{TTTA})_{11}\) alleles of the CYP19 (TTTA)_n tetranucleotide repeat polymorphism in intron 4 have been associated with prostate cancer risk in one study (37) but we failed to find any effect (38). The COMT Val158Met polymorphism has only been examined in one Japanese population and no association with prostate cancer was observed (39).

Polymorphisms in genes involved in BER have been evaluated mainly in lung cancer (40,41) because large quantities of ROS can also be generated by constituents of cigarette smoke (42). However, genetic variants in BER have not been well studied in prostate cancer. Two studies have reported an association between the hOGG1 Ser326Cys polymorphism and prostate cancer but the results are equivocal (43,44). Although we (45) and Van Gils et al. (46) failed to find a statistically significant association between the XRCC1 Arg399Gln polymorphism and prostate cancer but the results are equivocal (43,44). Although we (45) and Van Gils et al. (46) failed to find a statistically significant association between the XRCC1 Arg399Gln polymorphism and prostate cancer but the results are equivocal (43,44). Although we (45) and Van Gils et al. (46) failed to find a statistically significant association between the XRCC1 Arg399Gln polymorphism and prostate cancer but the results are equivocal (43,44). Although we (45) and Van Gils et al. (46) failed to find a statistically significant association between the XRCC1 Arg399Gln polymorphism and prostate cancer but the results are equivocal (43,44).

To further investigate the potential effects of oxidized estrogen metabolites in prostate cancer, we evaluated polymorphisms in catechol estrogen detoxification (COMT Val158Met) and oxidative DNA base lesion repair (hOGG1 Ser326Cys) in a family (sibling) based case–control study. We also examined possible joint effects between these polymorphisms and smoking and between these polymorphisms and others previously

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Fig. 1. Estrogen bioactivation, detoxification and base excision repair (BER) of potential oxidative DNA base damage. Enzymes involved in hormone metabolism, detoxification and BER repair are shown in red, green, and blue, respectively. Large quantities of ROS such as the superoxide anion \( \ce{O_2^{-\cdot}} \) may be generated by futile redox cycling of catechol estrogen and quinone metabolites. ROS may cause a spectrum of damage including oxidative DNA base damage (e.g. 8-oxo-dG); however, this damage may be repaired by enzymes in the short patch BER pathway.
examined in this study population that may also play a role in estrogen bioactivation [CYP19 (TTTA)$_n$ and CYP1B1 Leu432Val] and BER (XRC1 Arg399Gln).

Materials and methods

Study population

The study design and population have been described elsewhere (47). Briefly, men with prostate cancer ($n = 439$) and their unaffected brothers ($n = 479$) were recruited from the major medical institutions in Cleveland, OH, and from the Henry Ford Health System in Detroit, MI. Of the 413 families participating in the study, $\sim 90\%$ were Caucasian, $9\%$ African-American and $1\%$ were Asian or Latino. Institutional Review Board approval was obtained from all participating institutions. All study subjects provided informed consent.

PCR products were digested by restriction enzyme digestion, and the clinical characteristics were obtained from medical records. PSA testing was conducted in unaffected sibling(s) and any of these men with a PSA > 4 mg/ml were notified by one of the collaborating urologists and followed to confirm their disease-free status. All unaffected brothers were no more than 8 years younger than their affected brother(s) and the median time between case diagnosis and recruitment into the study was 2 years.

Demographic (age) and smoking information was determined from a self-administered health and habits questionnaire. Subjects who reported smoking cigarettes regularly for a total of 6 months or longer were considered smokers. Light and heavy smokers were classified as those subjects who smoked $< 1$–20 pack-years and $> 20$ pack-years, respectively.

Genotyping

Standard venipuncture was used to collect blood samples from all study participants in tubes with EDTA as an anticoagulant. Genomic DNA was extracted fromuffy coats using the QIAamp DNA Blood kit (QIAGEN Inc, Valencia, CA). All purified DNA samples were diluted to a constant DNA concentration in 10 mM Tris, 1 mM EDTA buffer (pH 8).

The presence of the COMT Val158Met (rs6680) polymorphism was detected by amplifying genomic DNA with the forward primer 5'-TCTGGGA-CGCCGTGATTCCGGG-3' and the reverse primer 5'-AGGTTCTGACACGGGCCAGGCTGAGT-3'. The polymerase chain reaction (PCR) amplification parameters were a 5 min initial denaturation cycle at 94°C, and 30 cycles each of 30 s at 94°C, 30 s at 55°C and 30 s at 72°C, followed by a 7 min final elongation cycle at 72°C. The 217 bp PCR product was digested with NlaIII (New England Biolabs, Beverly, MA) at 37°C for 1 h. Digested products were separated by electrophoresis and visualized by ethidium bromide staining. Wild-type alleles resulted in 114 bp, 82 bp, and 20 bp fragments and the variant allele resulted in 96 bp, 82 bp, 20 bp, and 18 bp fragments following restriction enzyme digestion.

The presence of the hOGG1 Ser326Cys (rs1052133) polymorphism was detected by amplifying genomic DNA with the forward primer 5'-ACTGTACTAGTCTACCAG-3' and the reverse primer 5'-GAGAAGTGCTTGGGAAAT-3'. The PCR amplification parameters were a 5 min initial denaturation cycle at 94°C, and 30 cycles each of 1 min at 94°C, 1 min at 58°C and 2 min at 72°C, followed by a 7 min final elongation cycle at 72°C. The 201 bp PCR product was digested with Fnu4HI (New England Biolabs, Beverly, MA) at 37°C for 1 h. Digested products were separated by electrophoresis and visualized by ethidium bromide staining. Wild-type alleles resulted in 101 bp and the variant allele resulted in 100 bp and 101 fragments following restriction enzyme digestion.

To ensure quality control of all genotyping results, 5% of the samples were randomly selected and genotyped by a second investigator and 1% of the samples were sequenced using a 377 ABI automated sequencer.

Statistical analysis

We first calculated genotype frequencies and tested for Hardy–Weinberg Equilibrium (HWE) within the major ethnic groups (i.e. Caucasian and African-American) among controls. We then used conditional logistic regression (with family as the matching variable) to estimate ORs and 95% CIs for the association between genotypes, smoking and prostate cancer. To address the potential for additional familial correlation induced by matching on sibship, a robust covariance estimator (48) was used in the conditional logistic regression analysis. We also investigated modification of the effects by disease aggressiveness using the criteria, determined a priori, of Rebbeck et al. (49), where low aggressive disease was defined as having a Gleason score (GS) < 7 and a clinical tumor stage (CTS) < T2c for all cases in the sibship, and high aggressive disease was characterized as having a GS $\geq 7$ or a CTS $\geq T2c$ for at least one case in the sibship. Moreover, we examined the interaction between smoking and genetic factors using a conditional logistic regression model (with the robust covariance estimator described above) that included both main effect terms and term(s) for their multiplicative interaction(s). All results are adjusted for age (using age at diagnosis for cases and age at enrollment for controls). All $P$-values are from two-sided tests. All analyses were undertaken with SAS (Version 8.2, SAS Institute, Cary, NC).

Results

Characteristics of the study population are provided in Table I. The population was $\sim 90\%$ Caucasian and the mean age of cases (61.5 years) was slightly younger than that of controls (62.8 years). Approximately 44% of the cases had a GS of greater than or equal to 7 and 13% had a CTS of T2c or greater, resulting in about half of the cases having more aggressive disease (GS $\geq 7$ or CTS $\geq T2c$). The frequency of smoking was not materially different between cases and controls (Table I).

All genetic variants were in Hardy–Weinberg equilibrium within ethnic groups. Ignoring the matching, there were no statistically significant allele frequency differences between cases and controls (Table I). The COMT 158Met and hOGG1 326Cys variant allele frequencies we observed among Caucasian controls in our study population were generally consistent with prior reports in Caucasian men in the general population (50,51).

Neither the COMT Val158Met nor the hOGG1 Ser326Cys polymorphism was associated with prostate cancer risk in the total study population (Table II). However, among men with more aggressive disease, there was an inverse association between prostate cancer and carrying the hOGG1 326Cys/Cys genotype compared with the Ser/Ser genotype (OR = 0.30; 95% CI: 0.09–0.98; $P = 0.05$). A slightly weaker effect was found between the hOGG1 326Cys/Cys genotype and prostate cancer risk when using a recessive genetic model (OR = 0.34; 95% CI: 0.11–1.04; $P = 0.06$) and when restricting the analysis to Caucasians only (OR = 0.35; 95% CI: 0.10–1.21; $P = 0.09$). Among men with more aggressive disease, there was an inverse association between smoking and carrying the hOGG1 326Cys/Cys genotype compared with the Ser/Ser genotype (OR = 0.34; 95% CI: 0.11–1.04; $P = 0.06$) and when restricting the analysis to Caucasians only (OR = 0.35; 95% CI: 0.10–1.21; $P = 0.09$). Among men with more aggressive disease, there was an inverse association between smoking and carrying the hOGG1 326Cys/Cys genotype compared with the Ser/Ser genotype (OR = 0.34; 95% CI: 0.11–1.04; $P = 0.06$) and when restricting the analysis to Caucasians only (OR = 0.35; 95% CI: 0.10–1.21; $P = 0.09$). Among men with more aggressive disease, there was an inverse association between smoking and carrying the hOGG1 326Cys/Cys genotype compared with the Ser/Ser genotype (OR = 0.34; 95% CI: 0.11–1.04; $P = 0.06$) and when restricting the analysis to Caucasians only (OR = 0.35; 95% CI: 0.10–1.21; $P = 0.09$).

Table I. Characteristics of the family-based case–control study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 439)</th>
<th>Controls (n = 479)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>61.5 (6.7)$^a$</td>
<td>62.8 (9.1)$^a$</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>397 (90)</td>
<td>437 (91)</td>
</tr>
<tr>
<td>African-American</td>
<td>38 (9)</td>
<td>38 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>GS $\geq$ 7</td>
<td>191 (44)</td>
<td>–</td>
</tr>
<tr>
<td>CTS $\geq$ T2c</td>
<td>55 (13)</td>
<td>–</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers</td>
<td>278 (63)</td>
<td>304 (64)</td>
</tr>
<tr>
<td>Light smokers$^b$</td>
<td>114 (27)</td>
<td>125 (27)</td>
</tr>
<tr>
<td>Heavy smokers$^b$</td>
<td>154 (36)</td>
<td>170 (36)</td>
</tr>
<tr>
<td>Genotypes (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hOGG1 Ser326Cys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>280 (63.8)</td>
<td>305 (63.8)</td>
</tr>
<tr>
<td>Ser/Cys</td>
<td>135 (30.7)</td>
<td>142 (29.7)</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>24 (5.5)</td>
<td>31 (6.5)</td>
</tr>
<tr>
<td>COMT Val158Met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val/Val</td>
<td>116 (26.4)</td>
<td>124 (25.9)</td>
</tr>
<tr>
<td>Val/Met</td>
<td>214 (48.8)</td>
<td>238 (49.7)</td>
</tr>
<tr>
<td>Met/Met</td>
<td>109 (24.8)</td>
<td>117 (24.4)</td>
</tr>
</tbody>
</table>

$^a$Value in parentheses is the standard deviation of the mean.

$^b$Light smokers, $\leq$20 pack-years; Heavy smokers, $>20$ pack-years.
disease, a higher risk of prostate cancer was observed in those carrying two copies of the 158Met allele compared with those with two copies of the 159Val wild-type allele but this was not statistically significant (Table II). Adjustment for smoking did not materially alter results and no statistically significant interaction with the hOGG1 Ser326Cys or COMT Val158Met polymorphisms and smoking was observed using continuous (pack-years) or categorical [e.g., ever versus never, light (≤20 pack-years) and heavy (>20 pack-years) versus never] variable forms (not shown).

We also examined joint gene effects based upon the enzyme’s function in the pathway (Figure 1) and the amino acid’s hypothesized activity level. For example, the biological interaction between hOGG1 and XRCC1 is well documented (52) and there is evidence suggesting that the XRCC1 399Arg wild-type allele (53). Therefore, we combined the low-activity COMT Val158Met and hOGG1 Ser326Cys genotypes in the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys) combination also resulted in a decreased prostate cancer risk among men with more aggressive disease (OR = 0.01–0.56; P = 0.01). Including the XRCC1 399Arg/Arg or Arg/Gln genotypes in the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys) combination also resulted in a decreased prostate cancer risk among men with more aggressive disease (Table III), particularly among Caucasian men with more aggressive disease (OR = 0.08; 95% CI: 0.01–0.53; P = 0.01). Including the high-activity COMT 158Val allele to the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys) combination (OR = 0.19; 95% CI: 0.04–0.82; P = 0.02) and the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys)-XRCC1 (399 Arg/Arg or Arg/Gln) combination (OR = 0.20; 95% CI: 0.05–0.88; P = 0.03) also resulted in decreased prostate cancer risk among men with more aggressive disease but the reduction in risk was not as notable as that observed when 158Val was excluded and not materially altered by restricting to Caucasians only.

### Discussion

We found that the hOGG1 326 Cys/Cys genotype compared with the Ser/Ser genotype was inversely associated with prostate cancer risk among men with more aggressive disease. Xu et al. (43) observed a similar effect but they used the more common allele as the referent group and reported an increased prostate cancer risk with the hOGG1 326 Cys/Cys genotype. However, Chen et al. (44) reported that carrying one or two copies of the hOGG1 326Cys allele increased prostate cancer risk when they adjusted for age and smoking. Stratification by smoking status revealed that the increased risk observed by Chen et al. (44)

### Table II. ORs for polymorphisms in catechol estrogen inactivation and BER genes and prostate cancer

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>ORs (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT Val158Met</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td>Val/Val</td>
<td>1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Caucasians only</td>
<td>Val/Val</td>
<td>1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Low aggressive</td>
<td>Val/Val</td>
<td>1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Low aggressive (Caucasians only)</td>
<td>Val/Val</td>
<td>1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>hOGG1 Ser326Cys</td>
<td>Ser/Ser</td>
<td>1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>All subjects</td>
<td>Ser/Ser</td>
<td>1.00</td>
<td>0.71</td>
</tr>
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<tr>
<td>Low aggressive (Caucasians only)</td>
<td>Ser/Ser</td>
<td>1.00</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*All results include adjustment for age.

*Includes cases with GS ≤ 7 and a CTS ≤ T2C and their brothers.

*Includes cases with GS ≥ 7 or a CTS > T2C and their brothers.

*Recessive model (Cys/Cys versus Ser/Ser or Ser/Cys): OR = 0.34 (0.11–1.04); P = 0.06.

*Recessive model (Cys/Cys versus Ser/Ser or Ser/Cys): OR = 0.39 (0.11–1.34); P = 0.13.
was only statistically significant in ever smokers. We did not observe any confounding or effect modification of the hOGG1 Ser326Cys association by smoking. Although our study and the two prior studies evaluating the hOGG1 Ser326Cys polymorphism and prostate cancer were comprised predominantly of Caucasians, our sample size was much larger. Furthermore, unlike the prior population-based studies, our family (sibling) based case–control study is not susceptible to population stratification.

Although hOGG1 is abundantly expressed in prostate tissue (43), the functional consequences of the hOGG1 Ser326Cys polymorphism are strongly debated (51). Initially, the hOGG1 Ser326Ser enzyme was shown to have higher activity than the 326Cys variant enzyme (57) but others have not been able to replicate this (58). If the hOGG1 326Cys allele does result in higher activity, the Cys/Cys genotype would be protective as men with more aggressive disease—the first two being particularly notable in Caucasians. Although no prior studies have reported on these specific genotype combinations, the reduced risks are biologically plausible. As shown in Figure 1, lower activity in CYP1B1 (conferred by carrying the 432Leu allele) and higher activity in COMT (conferred by carrying the 158Val allele) would presumably result in lower levels of catechol estrogen, which, in turn, would decrease the amount of ROS generated from futile redox cycling between the catechol estrogen and their quinone metabolites. Moreover, CYP1B1 is highly expressed in the prostate (60,61), particularly in the peripheral zone where most cancers arise (62). Although no prior studies have reported on these specific genotype combinations, the reduced risks are biologically plausible. As shown in Figure 1, lower activity in CYP1B1 (conferred by carrying the 432Leu allele) and higher activity in COMT (conferred by carrying the 158Val allele) would presumably result in lower levels of catechol estrogen, which, in turn, would decrease the amount of ROS generated from futile redox cycling between the catechol estrogen and their quinone metabolites. Moreover, CYP1B1 is highly expressed in the prostate (60,61), particularly in the peripheral zone where most cancers arise (62). Although no prior studies have reported on these specific genotype combinations, the reduced risks are biologically plausible. As shown in Figure 1, lower activity in CYP1B1 (conferred by carrying the 432Leu allele) and higher activity in COMT (conferred by carrying the 158Val allele) would presumably result in lower levels of catechol estrogen, which, in turn, would decrease the amount of ROS generated from futile redox cycling between the catechol estrogen and their quinone metabolites. Moreover, CYP1B1 is highly expressed in the prostate (60,61), particularly in the peripheral zone where most cancers arise (62). Although no prior studies have reported on these specific genotype combinations, the reduced risks are biologically plausible. As shown in Figure 1, lower activity in CYP1B1 (conferred by carrying the 432Leu allele) and higher activity in COMT (conferred by carrying the 158Val allele) would presumably result in lower levels of catechol estrogen, which, in turn, would decrease the amount of ROS generated from futile redox cycling between the catechol estrogen and their quinone metabolites. Moreover, CYP1B1 is highly expressed in the prostate (60,61), particularly in the peripheral zone where most cancers arise (62). Although no prior studies have reported on these specific genotype combinations, the reduced risks are biologically plausible.

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\begin{array}{lcccc}
\text{Genotype combination} & \text{Cases/controls} & \text{OR (95\% CI)} & \text{Cases/controls} & \text{OR (95\% CI)} & \text{P-value} \\
\hline
\text{Total population} & 417/450 & 1.00 (Referent) & 22/29 & 0.62 (0.26–1.48) & 0.28 \\
\text{Low aggressive} & 178/198 & 1.00 (Referent) & 10/9 & 1.55 (0.38–6.32) & 0.54 \\
\text{High aggressive} & 215/223 & 1.00 (Referent) & 10/17 & 0.26 (0.08–0.90) & 0.03 \\
\text{Total population} & 428/464 & 1.00 (Referent) & 11/15 & 0.62 (0.21–1.80) & 0.38 \\
\text{High aggressive} & 219/226 & 1.00 (Referent) & 7/16 & 0.13 (0.02–0.78) & 0.03 \\
\text{Low aggressive} & 202/220 & 1.00 (Referent) & 5/24 & 0.46 (0.17–1.24) & 0.13 \\
\text{Total population} & 424/455 & 1.00 (Referent) & 15/24 & 0.46 (0.17–1.24) & 0.13 \\
\text{Low aggressive} & 181/200 & 1.00 (Referent) & 7/7 & 1.17 (0.26–5.39) & 0.84 \\
\text{High aggressive} & 218/224 & 1.00 (Referent) & 6/14 & 0.14 (0.02–0.81) & 0.03 \\
\text{Total population} & 423/453 & 1.00 (Referent) & 16/26 & 0.44 (0.17–1.18) & 0.10 \\
\text{Low aggressive} & 181/200 & 1.00 (Referent) & 7/7 & 1.17 (0.26–5.39) & 0.84 \\
\text{High aggressive} & 217/223 & 1.00 (Referent) & 10/17 & 0.26 (0.08–0.90) & 0.03 \\
\text{Total population} & 423/453 & 1.00 (Referent) & 16/26 & 0.44 (0.17–1.18) & 0.10 \\
\text{Low aggressive} & 181/200 & 1.00 (Referent) & 7/7 & 1.17 (0.26–5.39) & 0.84 \\
\text{High aggressive} & 217/223 & 1.00 (Referent) & 10/17 & 0.26 (0.08–0.90) & 0.03 \\
\end{array}
\]

\(^{a}\) All models are adjusted for age.

\(^{b}\) Includes cases with GS < 7 and a CTS < T2C and their brothers.

\(^{c}\) Includes cases with GS ≥ 7 or a CTS ≥ T2C and their brothers.

\(^{d}\) Restriction to Caucasians only did not materially alter results.

\(^{e}\) Restriction to Caucasians only: 0.08 (0.01–0.53); P = 0.01.  

\(^{f}\) Restriction to Caucasians only: 0.09 (0.01–0.56); P = 0.01.

Table III. ORs for combinations of polymorphisms in estrogen bioactivation, inactivation and BER genes and prostate cancer

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presumably decrease the level of irreversible mutations and further reduce prostate cancer risk.

Experimental studies also support a role for catechol estrogen-induced ROS in prostate cancer, particularly more aggressive forms. Most notably, cells from LNCaP—a prostate cancer cell line derived from lymph node metastasis—stimulated with catechol estrogens have shown a dose-dependent increase in ROS and DNA damage (18). Malignant prostate cells were also found to have defective repair of oxidative DNA base damage; however, this occurred despite elevated expression of XRCC1 (66). A mechanistic study that more fully evaluates human variation in response to catechol estrogen-induced ROS damage and repair, particularly in the presence of chronic inflammation, which can exacerbate ROS-related DNA damage in the prostate (18,67), would help clarify the potential relations we observed.

In summary, the role of estrogens in prostate cancer is not well understood but catechol estrogens may generate large quantities of ROS and oxidative DNA damage. We found a decreased risk associated with the hOGG1 326 Cys/Cys genotype and a further reduced risk with the CYP1B1 (432 Leu/Leu or Leu/Val)-hOGG1 (326 Cys/Cys)-XRCC1 (399 Arg/Arg or Arg/Gln) genotype combination among men with more aggressive prostate cancer, which may lend new insights to the importance of ROS generated from non-receptor-mediated estrogenic mechanisms in aggressive prostate cancer.

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References


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