Polymorphic variants in PTGS2 and prostate cancer risk: results from two large nested case–control studies

Kim N. Danforth1, *, Richard B. Hayes1, Carmen Rodriguez2, Kai Yu1, Lori C. Sakoda1, Wen-Yi Huang3, Bingshu E. Chen4, Jinbo Chen5, Gerald L. Andrelo6, Eugenia E. Call6, Eric J. Jacobs7, Lisa W. Chu7, Jonine D. Figueroa1,7, Meredith Yeager5, Elizabeth A. Platz8, Dominique S. Michaud9, Stephen J. Chanock1,8,11, Michael J. Thun2 and Ann W. Hsing1

1 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20852; 2 Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA 30303; 3 Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195; 4 Department of Mathematics and Statistics, Concordia University, Montreal, Quebec H3G IM8, Canada; 5 Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; 6 Department of Urologic Surgery, Washington University School of Medicine, St Louis, MO 63110; 7 Cancer Prevention Fellowship Program, Office of Preventive Oncology, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20852; 8 Core Genotyping Facility, Division of Cancer Epidemiology and Genetics, Advanced Technology Program, SAIC Frederick, Inc., NCI-Frederick, Frederick, MD 20877; 9 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; 10 Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115 and 11 Center for Cancer Research, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892

*To whom correspondence should be addressed. Tel: +1 301 594 5631; Fax: +1 301 402 0916; Email: danforth@mail.nih.gov

Chronic inflammation has been hypothesized to increase prostate cancer risk. Prostaglandin-endoperoxide synthase 2 (PTGS2) encodes the proinflammatory cyclooxygenase 2 enzyme believed to be the rate-limiting step in the synthesis of prostaglandins, important mediators of inflammation. We investigated associations between PTGS2 polymorphisms and prostate cancer risk among 2321 prostate cancer cases and 2560 controls in two large case–control studies nested within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the Cancer Prevention Study II (CPS-II) Nutrition Cohort. Five single nucleotide polymorphisms (SNPs) in 1086 inflammatory genes were examined in SNP and haplotype analyses (five SNPs in PLCO and four SNPs in the Nutrition Cohort). In PLCO, the Ex10 +837 T>C marker was initially associated with prostate cancer risk (P-trend = 0.02) but became non-significant after adjustment for multiple comparisons (P = 0.08); this SNP showed no association with prostate cancer risk in the Nutrition Cohort (P-trend = 0.54) or in an analysis pooling the two cohorts (P-trend = 0.20). No other SNP was associated with prostate cancer risk in PLCO or the Nutrition Cohort individually or combined. Haplotype analyses suggested an association between PTGS2 variants in PLCO alone (global P = 0.007), but not in the Nutrition Cohort (global P = 0.78) or pooled analysis (global P = 0.18). In conclusion, despite the potential importance of inflammation in prostate carcinogenesis, results from our large study of five PTGS2 SNPs does not support a strong association between PTGS2 variants and prostate cancer risk in non-Hispanic white men.

Introduction

The prostaglandin-endoperoxide synthase 2 (PTGS2) gene encodes the proinflammatory cyclooxygenase 2 enzyme believed to be the rate-limiting step in the synthesis of prostaglandins, important mediators of inflammation (1). Chronic inflammation has been implicated in the development of several cancers, including prostate cancer (2,3), and proliferative inflammatory atrophy, an inflammatory condition in the prostate, has been hypothesized to be a precursor lesion for prostate cancer (4). Recently, a large Swedish study examined 9275 single nucleotide polymorphisms (SNPs) in 1086 inflammatory genes and reported significant (α = 0.01) associations between 106 SNPs and prostate cancer (5), suggesting that variation in inflammation genes may play a role in prostate cancer risk. Research on non-genetic factors, including non-steroidal anti-inflammatory drug (NSAID) use, obesity and prostatectomy, also supports a possible etiologic role for inflammation in prostate cancer risk (6–9).

Three previous studies have examined the relationships between various PTGS2 polymorphisms and prostate cancer risk (10–12) with mixed results. To further clarify the role of PTGS2 variants in prostate cancer development, we investigated associations between five PTGS2 polymorphisms and prostate cancer risk among 2321 prostate cancer cases and 2560 controls in two large case–control studies nested within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the Cancer Prevention Study II (CPS-II) Nutrition Cohort.

Materials and methods

Study participants

PLCO Cancer Screening Trial. The PLCO Cancer Screening Trial (hereafter referred to as PLCO) is an ongoing, randomized controlled trial designed to evaluate the impact of screening tests on cancer-specific mortality. Details on the trial have been published previously (13,14). From 1993–2001, 154 000 men and women, aged 55–74 years, were enrolled at 10 screening centers throughout the country (Washington, DC; Detroit, MI; Salt Lake City, UT; Denver, CO; Honolulu, HI; Minneapolis, MN; Marshfield, WI; Pittsburgh, PA; St Louis, MO; Birmingham, AL) and randomized to the trial’s screening arm or usual care. During screening visits, blood samples were collected. This analysis uses non-Hispanic white men from the screening arm of the trial. Institutional review boards at the National Cancer Institute (NCI) and each of the participating institutions approved the PLCO protocol, and each participant provided written informed consent.

Prostate tumors were identified by screening exams (prostate-specific antigen test, digital rectal exam), reports from participants, physicians or relatives, linkage with the National Death Index or linkage with state cancer registries. All cases were pathologically confirmed. Cases were classified as “advanced” if there was extraprostatic extension (stage III), metastasis (stage IV) or a Gleason score of ≥7 (using the highest available Gleason score and the best available information from pathology and/or clinical data for staging). Controls (n = 1399) were matched to cases (n = 1162) identified between October 1993 and September 2001 on age, time since initial screening and year of blood draw using incidence density sampling.

CPS-II Nutrition Cohort. The CPS-II Nutrition Cohort (hereafter referred to as the Nutrition Cohort) is a prospective cohort study designed to examine associations between a wide range of exposures and cancer incidence, as described previously (15). It was established by the American Cancer Society in 1992 and 1993 among 86 000 men and 97 000 women in 21 USA states (California, Connecticut, Florida, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Jersey, New Mexico, New York, North Carolina, Pennsylvania, Utah, Virginia, Washington, Wisconsin). Blood samples were collected from a subset of Nutrition Cohort participants between June 1998 and June 2001 (17 411 men and 21 965 women). This analysis uses non-Hispanic white men who provided a blood sample. The Emory University
Prostate cancers diagnosed between enrollment in the Nutrition Cohort and August 2001 were identified through self-report or National Death Index linkage and were subsequently confirmed by medical record review or registry linkage, except for two prostate cancer deaths for which information was available only from death certificates. Prostate cancer was classified as advanced if the Gleason score was ≥7, the tumor was classified as stage III or IV, or it was a metastatic case of unknown stage at diagnosis. Cases (n = 1159) and controls (n = 1161) were matched on age and date of blood collection using incidence density sampling.

Genotyping
SNPs were selected based on putative function, reported minor allele frequency (≥5%) and the availability of a validated assay at the NCI’s Core Genotyping Facility (http://snpg500cancer.nci.nih.gov). Five SNPs were genotyped in PLCO and four in the Nutrition Cohort (all also in PLCO) using the TaqMan assay. The genotyping completion rate was ≥98% in PLCO and >92% in the Nutrition Cohort. The interassay concordance from blinded quality control samples was >99% in both studies.

Many participants (~75%) in our original PLCO analysis had one of their SNPs (rs5275) genotyped again, using an Illumina assay, when they were later included in a genome-wide scan as part of the Cancer Genetic Markers of Susceptibility (CGEMS) Study (16,17). The CGEMS study, which oversampled advanced cancers, also genotyped several hundred additional PLCO participants who were identified during further follow-up and were not included in our original sample. For men assayed by both platforms (n = 1817), genotype concordance was >99.9% after excluding missing data (≤1.5% for each method).

Statistical analysis
For SNP analyses, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression models. In each study (PLCO and Nutrition Cohort), results from unadjusted and adjusted (for matching factors) models were similar; therefore, only unadjusted results are presented. The matching factors considered as covariates in adjusted models were age, smoking, race/ethnicity, and date of blood collection in the Nutrition Cohort.

Associations were calculated for each genotype (homozygote and heterozygote for the variant allele) separately and combined, compared with the reference genotype (homozygote for the most common allele). Tests for trend were based on the number of copies of the minor allele. For pooled analyses (PLCO and Nutrition Cohort), heterogeneity was assessed using a two degrees of freedom Wald test for gene-by-study interaction terms. Pooled analyses for rs5275 included PLCO participants with and without data from CGEMS and Nutrition Cohort participants.

Haplotype frequencies and ORs were estimated using the expectation-maximization algorithm in haplo.stats (R) (18) based on the four SNPs in both studies. Haplotype frequencies among controls were compared for PLCO and the Nutrition Cohort before pooling data; in the pooled analysis, heterogeneity by study was assessed using a global Wald test (19).

SNP analyses were adjusted for multiple testing using the Simes test, which is based on the test for linear trend using the number of copies of the minor allele. For pooled analyses (PLCO and Nutrition Cohort), heterogeneity was assessed using a two degrees of freedom Wald test for gene-by-study interaction terms. Pooled analyses for rs5275 included PLCO participants with and without data from CGEMS and Nutrition Cohort participants.

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SNP analyses were adjusted for multiple testing using the Simes test, which is based on the test for linear trend using the number of copies of the minor allele (0, 1 and 2) (20). A global score test by Schaid et al. (21) was used to test for overall differences in the frequency of the haplotypes between cases and controls.

Results
In each study, ~65% of study participants were between 60 and 70 years old (Table I). Men in both studies were highly educated, with >40% receiving at least a college degree. A little over half of participants reported use of NSAIDs. Men in the Nutrition Cohort were less likely to report a history of diabetes, but more likely to report a family history of prostate cancer, than men in PLCO.

Among controls, all polymorphisms were in Hardy–Weinberg equilibrium (P > 0.05). In PLCO, PTGS2 variants were not associated overall with prostate cancer risk (Table II). Although the CC genotype of the Ex10 +837T>C marker (rs5275) was initially associated with a 37% increased risk compared with the TT genotype, this association was not significant after adjustment for multiple testing (P = 0.08). Results for this SNP also became borderline significant (P-trend = 0.05) when >350 men genotyped through CGEMS were included (CC versus TT genotype, OR = 1.26, 95% CI: 0.98–1.60). No other SNP was significantly associated with prostate cancer risk in PLCO, although point estimates for three other SNPs (rs5277, rs20432 and rs468276) were similar to those observed for rs5275.

Table I. Characteristics of non-Hispanic white prostate cancer cases and controls in the PLCO Cancer Screening Trial and the CPS-II Nutrition Cohort

<table>
<thead>
<tr>
<th></th>
<th>PLCO Cases (n = 1162)</th>
<th>PLCO Controls (n = 1399)</th>
<th>Nutrition Cohort Cases (n = 1159)</th>
<th>Nutrition Cohort Controls (n = 1161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>183 (15.8)</td>
<td>215 (15.4)</td>
<td>196 (16.9)</td>
<td>210 (18.1)</td>
</tr>
<tr>
<td>55–59</td>
<td>364 (31.3)</td>
<td>435 (31.1)</td>
<td>391 (33.7)</td>
<td>381 (32.8)</td>
</tr>
<tr>
<td>60–64</td>
<td>396 (34.1)</td>
<td>490 (35.0)</td>
<td>390 (33.7)</td>
<td>390 (33.6)</td>
</tr>
<tr>
<td>65–69</td>
<td>219 (18.8)</td>
<td>259 (18.5)</td>
<td>124 (10.7)</td>
<td>126 (10.8)</td>
</tr>
<tr>
<td>70–74</td>
<td>25 (2.2)</td>
<td>33 (2.8)</td>
<td>16 (1.4)</td>
<td>18 (1.5)</td>
</tr>
<tr>
<td>75–81</td>
<td>15 (1.3)</td>
<td>20 (1.5)</td>
<td>10 (0.9)</td>
<td>11 (0.9)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>109 (9.4)</td>
<td>98 (7.0)</td>
<td>51 (4.4)</td>
<td>56 (4.8)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>198 (17.0)</td>
<td>256 (18.3)</td>
<td>147 (12.7)</td>
<td>182 (15.7)</td>
</tr>
<tr>
<td>Vocational or some college</td>
<td>359 (30.9)</td>
<td>470 (33.6)</td>
<td>276 (23.8)</td>
<td>278 (23.9)</td>
</tr>
<tr>
<td>College graduate or higher</td>
<td>494 (42.5)</td>
<td>574 (41.0)</td>
<td>680 (58.7)</td>
<td>637 (54.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>329 (28.3)</td>
<td>354 (25.3)</td>
<td>461 (39.8)</td>
<td>431 (37.1)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>594 (51.1)</td>
<td>715 (51.1)</td>
<td>578 (49.9)</td>
<td>562 (48.4)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>224 (19.3)</td>
<td>316 (22.6)</td>
<td>105 (9.1)</td>
<td>154 (13.3)</td>
</tr>
<tr>
<td>NSAIDb use</td>
<td>578 (49.7)</td>
<td>756 (54.0)</td>
<td>671 (57.9)</td>
<td>639 (55.0)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>77 (6.6)</td>
<td>129 (9.2)</td>
<td>45 (3.9)</td>
<td>58 (5.0)</td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td>132 (11.4)</td>
<td>97 (6.9)</td>
<td>257 (22.2)</td>
<td>133 (11.5)</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>492 (42.3)</td>
<td>434 (37.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Missing categories not shown.

All characteristics presented at baseline (1993–2001 in PLCO and 1992–1993 in the Nutrition Cohort), except for family history of prostate cancer in the Nutrition Cohort, which was updated in 1997, and percent of advanced tumors.

Regular NSAID use in PLCO and ever NSAID use in the Nutrition Cohort; ‘regular use’ was not specifically defined on the PLCO questionnaire.

Advanced cancer: PLCO, Gleason score ≥7 or stage III/IV cancer; Nutrition Cohort, Gleason score ≥7, stage III/IV cancer or fatal case of unknown stage at diagnosis.
Among Nutrition Cohort participants, no SNP was associated with prostate cancer risk, with all point estimates close to one. The Ex10 +837T→C marker (rs5275) that appeared suggestive in PLCO showed no relationship to prostate cancer risk in the Nutrition Cohort (TC versus TT genotype, OR = 0.95, 95% CI: 0.80–1.13; CC versus TT genotype, OR = 0.94, 95% CI: 0.70–1.25).

There was no statistical evidence of heterogeneity between results of these two cohorts (P-heterogeneity > 0.10); thus, data from the two studies were pooled. In the pooled analyses, no SNP was associated with prostate cancer risk (including rs5275, P-trend = 0.20).

Haplotype frequency was significantly different between cases and controls in PLCO (global P = 0.007), but not in the Nutrition Cohort (global P = 0.78) (Table II). Using the four SNPs in both PLCO and the Nutrition Cohort, haplotype frequencies were similar among controls (P = 0.32). As was done for the SNP analyses, data were pooled from the two studies in a combined haplotype analysis (P-heterogeneity = 0.05). In the pooled analysis, PTGS2 haplotypes were not associated with prostate cancer risk (global P = 0.18).

In PLCO, risk patterns were generally similar among non-NSAID and NSAID users (data not shown). However, in the Nutrition Cohort, risk estimates varied by NSAID use, although no PTGS2 SNP was significantly associated with prostate cancer risk among either non-NSAID or NSAID users. For example, for the Ex10 +837T→C marker (rs5275), among non-NSAID users point estimates suggested an increased risk of prostate cancer (CC versus TT genotype, OR = 1.32, 95% CI: 0.84–2.08; n = 50 cases and 42 controls), whereas among NSAID users point estimates suggested a decreased risk of prostate cancer (CC versus TT genotype, OR = 0.75, 95% CI: 0.51–1.09; n = 62 cases and 74 controls) with the variant allele. When non-advanced/advanced tumor status was accounted for in this analysis, results remained non-significant but point estimates were slightly stronger for the advanced tumors compared with non-advanced.

### Table II. ORs and 95% CIs for prostate cancer risk and PTGS2 polymorphisms among non-Hispanic white men in the PLCO Cancer Screening Trial and the CPS-II Nutrition Cohort

<table>
<thead>
<tr>
<th>PTGS2 polymorphisms</th>
<th>PLCO Cases (n = 1162)</th>
<th>PLCO Controls (n = 1399)</th>
<th>OR (95% CI)</th>
<th>Nutrition Cohort Cases (n = 1159)</th>
<th>Nutrition Cohort Controls (n = 1161)</th>
<th>OR (95% CI)</th>
<th>PLCO + Nutrition Cohort combined Cases (n = 2321)</th>
<th>PLCO + Nutrition Cohort combined Controls (n = 2560)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>794</td>
<td>995</td>
<td>Referent</td>
<td>787</td>
<td>810</td>
<td>Referent</td>
<td>1581</td>
<td>1805</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>314</td>
<td>351</td>
<td>1.12 (0.94–1.34)</td>
<td>322</td>
<td>296</td>
<td>1.12 (0.93–1.35)</td>
<td>636</td>
<td>647</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>39</td>
<td>35</td>
<td>1.40 (0.88–2.22)</td>
<td>22</td>
<td>34</td>
<td>0.67 (0.39–1.15)</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>GT or GC</td>
<td>304</td>
<td>353</td>
<td>1.10 (0.97–1.26)</td>
<td>344</td>
<td>330</td>
<td>1.07 (0.90–1.29)</td>
<td>697</td>
<td>716</td>
</tr>
<tr>
<td></td>
<td>IVS5 → 275T→G</td>
<td>570</td>
<td>570</td>
<td></td>
<td>570</td>
<td>570</td>
<td></td>
<td>570</td>
<td>570</td>
</tr>
</tbody>
</table>

**SNP results**

- Ex3 –8G>C (rs5277): 1.12 (0.94–1.34)
- GC: 1.40 (0.88–2.22)
- GT or GC: 1.10 (0.97–1.26)
- IVS5 → 275T→G: 1.15 (0.97–1.36)

**ORs and 95% CIs not shown for SNP analyses with fewer than five men in a cell or haplotype analyses where the haplotype frequency is <5%**.

**After adjustment for multiple comparisons, P-value = 0.08.**

**Genotyping data were available for additional PLCO participants (not included in the original analysis) through CGEMS.**

**Bold letters indicate SNP changes from the referent haplotype. Haplotype: rs5277, rs20432, rs5275 and rs689470; rare haplotypes not shown. In PLCO, the haplotype analysis with all five SNPs (rs5277, rs20432, rs4648276, rs5275 and rs689470) was nearly identical to the haplotype analysis using only the four SNPs shown.**
Discussion

In this nested case–control study of \(>2300\) prostate cancer cases, we did not observe significant associations between \(PTGS2\) variants and prostate cancer risk overall. Although SNP and haplotype findings were suggestive in PLCO, they did not persist after adjustment for multiple comparisons or the inclusion of additional PLCO participants available through CGEMS. SNP and haplotype results for four SNPs were null in the Nutrition Cohort and pooled data set, and they did not support an association between \(PTGS2\) variants and prostate cancer risk. Overall, we did not find a strong association between prostate cancer risk and the Ex10 +837T>C marker (rs5275), although SNP and haplotype results were somewhat suggestive in PLCO. The role of rs5275 has been investigated in two previous studies, one in Sweden \((n=2160)\) and one in the USA \((n=834)\) \((12)\), and in both studies, this SNP was not associated with prostate cancer risk. Other SNPs (rs689470, rs2777, rs4648276 and rs20432) in our analysis were also examined by previous studies. The Ex10 −90C>T marker (rs689470) showed no association in two USA studies \((12)\), including ours, but the variant \((T)\) allele of this marker was associated with a decreased risk of prostate cancer in a Swedish case–control study \((11)\). In addition, consistent with our results, no associations were observed for the Ex3 −8G>C (rs5277) marker in a USA study \((12)\) and the IVS7 +111T>C marker (rs4648276) in a Swedish study \((11)\). However, in contrast to our results, the Swedish study found an association for the IVS5 −275T>G marker (rs20432) with prostate cancer risk, although point estimates did not suggest a dose–response trend across copies of the variant allele \((11)\).

A SNP not included in our study, rs2745557, was included in two other studies \((11,12)\). This polymorphism had the strongest association among SNPs examined in a USA case–control study of advanced prostate cancer \((12)\), but no dose–response trend was observed across copies of the variant allele, and no association was found in the Swedish case–control study for this SNP with prostate cancer risk \((11)\). One other epidemiologic study reported associations for variants in the \(PTGS2\) promoter and prostate cancer risk, but risk could not be reliably evaluated among whites due to their small sample size \((n=92\) cases and 92 controls) and low minor allele frequencies \((\text{most } \leq 1\%)\) \((10)\).

No consistent association emerged for various \(PTGS2\) SNPs across multiple study populations. Thus, despite some suggestive findings in each of three studies \([our study, the USA case–control study \((12)\) and the Swedish case–control study \((11)\)]\), associations between \(PTGS2\) variants and prostate cancer risk do not appear robust. It is unclear why associations vary across studies. Within our own study, differences were observed across study populations (PLCO and Nutrition Cohort) despite relatively large sample sizes, similar allele frequencies and similar demographic characteristics \((\text{e.g. both highly educated, white, older men from multiple states in the USA})\). It is possible that the varying associations resulted from chance alone, as supported by the attenuation of results within PLCO when additional PLCO participants were added to our original analysis \((\text{who had genotyping data available through CGEMS for rs5275, the SNP whose association was initially significant})\). However, it is also possible that the varied findings reflect differences in unidentified characteristics \((\text{genes or lifestyle factors})\) that interact with \(PTGS2\) in affecting prostate cancer risk.

There was some suggestion that associations between the \(PTGS2\) SNPs and prostate cancer risk were different among non-NSAID and NSAID users in the Nutrition Cohort, although no SNP was significantly associated with prostate cancer risk. Similarly, another USA case–control study of advanced prostate cancer \((12)\) suggested possible differences in associations between \(PTGS2\) variants and prostate cancer risk by NSAID use. Although the interaction between rs2745557 and NSAID use was not statistically significant, point estimates for NSAID use were stronger \((\text{more inverse})\) among men with the homozygote genotype for the most common allele than among men with the variant allele \((OR=0.62 \text{ and } 0.86, \text{ respectively})\) \((12)\). Thus, interactions between \(PTGS2\) variants and NSAID use might be further examined in studies large enough to detect these gene–environment interactions.

A notable strength of our study is its relatively large size with \(>2300\) cases, providing sufficient power to detect modest main effects. Genotyping error in the study is low, as evidenced by the high genotyping success rates and high interassay concordance. However, one major weakness of our study is that, with five candidate SNPs, we had limited gene coverage of \(PTGS2\). Our analysis included two \((rs5277 \text{ and rs5275})\) of the four \((rs5277, rs5275, rs2066826 \text{ and rs2206593})\) \(PTGS2\) SNPs needed to capture common genetic variation \((\text{minor allele frequency } \geq 0.05)\) according to HapMap data, based on Caucasian Utah residents of northern and western Europe ancestry \((22)\). Furthermore, results from a recent genome-wide scan \((\text{CGEMS})\) in one of our study populations \((\text{PLCO})\) provided information on four additional \(PTGS2\) SNPs \((\text{rs2206593, rs10911905, rs2143417 and rs2383529})\) not included in our original PLCO analysis, one of which was identified in HapMap \((\text{rs2206593})\) as a tagging SNP. No significant associations with prostate cancer risk were observed for any of these \(PTGS2\) SNPs \((\text{all } P\)-values \(\geq 0.36)\) \((17)\), indicating that \(PTGS2\) is not associated with prostate cancer.

Another limitation is that we did not examine other types of genetic variation, such as deletions, insertions or tandem repeats, and it is possible that these types of genetic variation in the \(PTGS2\) gene are important. Furthermore, variations in other genes in the inflammation pathway may interact with variants in \(PTGS2\) to affect the risk of prostate cancer. Thus, future studies should seek to examine the combined effects of multiple genes in the inflammation pathway on prostate cancer risk.

In conclusion, despite the potential importance of inflammation in prostate carcinogenesis, results from our large study of five \(PTGS2\) SNPs do not support a strong association between \(PTGS2\) variants and prostate cancer risk in non-Hispanic white men. However, it is possible that \(PTGS2\) may interact with other genes or lifestyle factors, such as NSAID use, to influence prostate cancer risk. Larger studies will be needed to evaluate such interactions.

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References


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