Null Results in Brief

No Association of ApoE Genotype with Risk of Prostate Cancer: A Nested Case-Control Study

Hui Liu1,2,3, Irene M. Shui4, Elizabeth A. Platz5, Lorelei A. Mucci4,6, and Edward L. Giovannucci1,4,6

Abstract

Background: Previous studies found that low total cholesterol level was associated with a lower risk of high-grade prostate cancer. Apolipoprotein E (ApoE) isoform is associated with total cholesterol level. The aim of this study was to explore associations of ApoE isoforms with prostate cancer risk.

Methods: We assessed ApoE genotypes and risk of prostate cancer in a prospective case-control study nested among men who provided a blood sample in 1993–95 within the Health Professionals Follow-up Study. We identified 1,169 incident cases of prostate cancer and 1,233 controls in follow-up through 2004. Associations of ApoE isoform and prostate cancer incidence were evaluated by logistic regression models.

Results: We found no statistically significant associations of ApoE variants with overall prostate cancer or Gleason sum ≤ 7 (3+4), Gleason sum ≥ 7 (4+3), clinically localized stage, or progression to metastasis or death. There was no evidence of effect modification by circulating total cholesterol or use of cholesterol-lowering drugs prior to diagnosis.

Conclusions: ApoE variants were not associated with the risk of prostate cancer or aggressive disease.

Impact: Our findings suggest that the mechanism of circulating cholesterol level affecting prostate cancer incidence may not rely on ApoE isoforms. Cancer Epidemiol Biomarkers Prev; 24(10): 1632–4. ©2015 AACR.

Introduction

The Apolipoprotein E (ApoE) gene is polymorphic with three major isoforms (e2, e3, and e4), forming six inherited combinations (e3e3, e4e4, e2e2, e3e4, e2e3, and e3e4) that are known to affect protein structure and function (1). The E4 allele has been associated with a higher serum level of total cholesterol (1). Given that cholesterol level has been related with risk of high-grade prostate cancer (2), variations in ApoE could explain some of this association. A few studies have investigated this association, but the conclusions are inconsistent, because the sample sizes were relatively small and they were unable to assess high-grade or lethal disease, and did not include information about circulating cholesterol or use of cholesterol lowering drugs (3–6). In the current study, we investigated whether ApoE isoforms are associated with total and aggressive prostate cancer incidence and, further, assessed modification by circulating cholesterol or cholesterol-lowering drugs.

Materials and Methods

Study population

This case-control study was nested within the Health Professionals Follow-up Study (HPFS; ref. 2), a prospective cohort study that enrolled 51,529 men ages 40 to 75 in 1986. Among 18,018 men who provided a blood sample in 1993–95, we identified 1,169 incident prostate cancer cases and 1,233 controls through 2004. This investigation was approved by the Institutional Review Board at the Harvard School of Public Health.

Apolipoprotein E genotyping

DNA extraction and genotyping have been previously reported (7). The ApoE isoform was determined using two SNPs (rs429358 and rs7412). Participants were divided into three groups according these genotypes: e3e3 (ApoE E3E3), e2e2/e2e3 (ApoE E2 carrier), and e4e4/e3e4 (ApoE E4 carrier). The e2e4 isoform was excluded due to small numbers. The frequency of these groups in controls was ApoE E3E3: 62%, E2 carriers: 14%, and E4 carriers: 24%. As expected, E4 carriers had the highest mean circulating cholesterol (201.8 mg/dL), followed by E3E3 (200.6 mg/dL) and E2 (192.3 mg/dL; refs. 1, 4).

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations of overall prostate cancer, Gleason sum ≤ 7 (3+4), Gleason sum ≥ 7 (4+3), clinically localized disease, and lethal disease. To assess effect modification by circulating total cholesterol concentration (dichotomized at the median), and use of cholesterol-lowering drugs prior to diagnosis (ever vs. never), we
conducted stratified analyses. All analyses were conducted using SAS 9.3 (SAS Institute). Power calculations were done using Power and Sample Size Software (NCSS). Tests for significance were two-sided with a P value of <0.05 considered statistically significant.

Results
The average age at diagnosis was 69.6 years; 86% had clinically localized prostate cancer, 17% had Gleason sum ≥7 (4+3) disease, and 9% had lethal disease (Supplementary Table 1). There were no statistically significant associations between ApoE genotype and risk of overall, Gleason sum/C21, clinically localized, and lethal prostate cancer (Table 1). Circulating cholesterol concentration or cholesterol-lowering drugs (Table 2) did not modify the association between ApoE isoforms and prostate cancer risk (all P_interaction > 0.07).

Discussion
The current study was the largest study to examine the association between ApoE and risk of prostate cancer. This

Table 1. ORs of prostate cancer by ApoE genotype, Health Professionals Follow-up Study

<table>
<thead>
<tr>
<th>Prostate cancer</th>
<th>ApoE genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>e3e3</td>
</tr>
<tr>
<td>Cases/controls, n</td>
<td>704/767</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Gleason sum ≤ 7 (4+3)</td>
<td>545/767</td>
</tr>
<tr>
<td>Cases/controls, n</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Gleason sum ≥ 7 (4+3)</td>
<td>103/767</td>
</tr>
<tr>
<td>Cases/controls, n</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Clinically localizeda</td>
<td>564/767</td>
</tr>
<tr>
<td>Cases/controls, n</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Lethalb</td>
<td>73/767</td>
</tr>
<tr>
<td>Cases/controls, n</td>
<td>1.00 (ref.)</td>
</tr>
</tbody>
</table>

aEstimated from an unconditional logistic regression model and adjusted for age at blood draw and time from blood draw to diagnosis.
bClinically localized disease indicates TNM stage being T1b to T2b and N0 and M0. Lethal prostate cancer includes prostate tumors with distant metastases at diagnosis, or progression to bone and/or organ metastases or prostate cancer-specific death during follow-up through January 31, 2012.

Table 2. Associations of ApoE genotype with the risk of prostate cancer, stratified by circulating cholesterol concentrationb and use of cholesterol-lowering drugs prior to diagnosisc, Health Professionals Follow-up Study

| Outcome | Circulating cholesterol concentration | | | Use of cholesterol-lowering drugs prior to diagnosis |
|---------|---------------------------------------| | | Total |
| | <Median | ≥Median | | Never | Ever |
| | Cases/controls, n | OR (95% CI) | Cases/controls, n | OR (95% CI) | Cases/controls, n | OR (95% CI) |
| | 355/377 | 1.00 (ref.) | 114/100 | 1.25 (0.90–1.68) | 131/156 | 1.06 (0.79–1.41) |
| | 345/385 | 1.00 (ref.) | 68/69 | 1.05 (0.73–1.52) | 150/154 | 1.08 (0.82–1.41) |
| | 262/385 | 1.00 (ref.) | 52/69 | 1.06 (0.71–1.57) | 112/154 | 1.05 (0.78–1.40) |
| | 47/377 | 1.00 (ref.) | 15/100 | 1.30 (0.69–2.44) | 22/136 | 1.31 (0.76–2.28) |
| | 56/385 | 1.00 (ref.) | 12/69 | 1.11 (0.57–2.19) | 32/154 | 1.45 (0.90–2.33) |
| | 282/377 | 1.00 (ref.) | 92/100 | 1.25 (0.90–1.73) | 107/136 | 1.09 (0.80–1.47) |
| | 276/385 | 1.00 (ref.) | 56/69 | 1.09 (0.74–1.60) | 125/154 | 1.12 (0.84–1.50) |
| | 34/377 | 1.00 (ref.) | 9/100 | 1.19 (0.54–2.64) | 13/156 | 1.04 (0.52–2.08) |
| | 35/385 | 1.00 (ref.) | 6/69 | 0.79 (0.32–1.96) | 11/154 | 0.72 (0.36–1.46) |

 Estimated from an unconditional logistic regression model and adjusted for age at blood draw and time from blood draw to diagnosis.

bCholesterol level for 21 individuals was not available. Median of cholesterol by batch was: 1996: 216.3 mg/dL; 1998: 210.9 mg/dL; 2000: 164.4 mg/dL; 2004: 202.0 mg/dL.

For controls, using the diagnosed date of their matched cases.

cClinically localized disease indicates TNM stage being T1b to T2b and N0 and M0. Lethal prostate cancer includes prostate tumors with distant metastases at diagnosis, or progression to bone and/or organ metastases or prostate cancer-specific death during follow-up through January 31, 2012.
study had a greater than 81% power to detect an OR of 1.40. We did not observe any significant associations between ApoE genotype and prostate cancer. A nonsignificant but suggestive increased risk of high-grade prostate cancer was observed in E4 carriers, but no corresponding increase in lethal disease was apparent. Only a few prior studies have investigated this association. One study from Finland indicated no difference in ApoE E4 frequency between those with prostate cancer (N = 130) and those with benign prostatic hyperplasia (N = 201) or controls (N = 259; ref. 5). A Norwegian study found no significantly different distribution in the frequency of the e4 allele among 230 prostate cancer cases and 798 controls (6). A study involving 35 men with prostate cancer reported an increased frequency of e4 allele (prevalence = 0.24) compared with the frequency in the general population (prevalence = 0.135 or 0.138; ref. 4). In addition, a multicountry ecological study also found that ApoE E4 was significantly correlated with prostate cancer incidence (3). Observations from prostate cancer cell lines provide evidence for a biologic mechanism of ApoE variants promoting aggressive prostate cancer via deregulating cholesterol homeostasis, although other differences could explain the differences in aggressive potential across these cell lines (8).

Our study had several strengths, including long follow-up time, detailed clinical information on the tumors, and the ability to assess whether the association was modified by total cholesterol level or use of cholesterol-lowering drugs. Limitations of the study were the inability to assess the ApoE e2e4 isoform, which has been found in aggressive cell lines (8), and the limited sample size to assess lethal disease.

In conclusion, this prospective study does not support the hypothesis that genetic variation in ApoE is appreciably associated with prostate cancer incidence or aggressiveness.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Disclaimer
None of the sponsors played a role in the study design, collection, analysis, and interpretation of the data, in the writing of this report, or in the decision to submit the paper for publication. The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors’ Contributions
Conception and design: H. Liu, I.M. Shui, E.A. Platz, E.L. Giovannucci
Development of methodology: I.M. Shui, E.L. Giovannucci
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I.M. Shui, E.A. Platz, L.A. Mucci, E.L. Giovannucci
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Liu, I.M. Shui, E.L. Giovannucci
Writing, review, and/or revision of the manuscript: H. Liu, I.M. Shui, E.A. Platz, L.A. Mucci, E.L. Giovannucci

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References
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