HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2015 October ; 24(10): 1632–1634. doi: 10.1158/1055-9965.EPI-15-0367.

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

Hui Liu[1,3,4], **Irene M. Shui**[2], **Elizabeth A. Platz**[5], **Lorelei A. Mucci**[2,6], and **Edward L. Giovannucci**[1,2,6]

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang University, Hangzhou, China

[4]Chronic Disease Research Institute, School of Public Health, Zhejiang University, Hangzhou, China

[5]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[6]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Previous studies found 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 Health Professionals Follow-up Study. We identified 1169 incident cases of prostate cancer and 1233 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.

Correspondence to: Edward L. Giovannucci, Departments of Epidemiology & Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA, 02115, USA, Tel: 617-432-4648, Fax: 617-432-2435, egiovann@hsph.harvard.edu.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Impact—Our findings suggest that the mechanism of circulating cholesterol level affecting prostate cancer incidence may not rely on ApoE isoforms.

Keywords

ApoE; Prostate Cancer; Nested Case-Control Study

Introduction

The *Apolipoprotein E (ApoE)* gene is polymorphic with 3 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, since 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 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.

Methods

Study population

This case-control study was nested within the Health Professionals Follow-up Study (HPFS) (2), a prospective cohort study that enrolled 51,529 men aged 40–75 in 1986. Among 18,018 men who provided a blood sample in 1993–95 we identified 1169 incident prostate cancer cases and 1233 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) (1,4).

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) 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,

Cary, NC). Power calculations were done using Power and Sample Size Software (NCSS, Kaysville UT).Tests for significance were two-sided with a p-value < 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 ≤ 7 (3+4), Gleason sum ≥ 7 (4+3), 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. Our study had adequate power to detect an odds ratio of 1.84 for the effect of genotype. We did not observe any significant associations between *ApoE* genotype and prostate cancer. A non-significant 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 E*4 frequency between those with prostate cancer (N=130) and those with benign prostatic hyperplasia (N=201) or controls (N=259) (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 to the frequency in general population (prevalence=0.135 or 0.138) (4). In addition, a multi-country ecological study also found *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, though 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This study was funded by National Cancer Institute grants: 1R01 CA133891-01A1, P01 CA55075, UM1 CA167552 and P30 CA006973. 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. Furthermore, the financial support from the China Scholarship Council (CSC) during a visit of H Liu to Harvard University was acknowledged. I.M. Shui was supported by a US Army Department of Defense Prostate Cancer Postdoctoral Fellowship.

References

1. Tao QQ, Chen Y, Liu ZJ, Sun YM, Yang P, Lu SJ, et al. Associations between apolipoprotein E genotypes and serum levels of glucose, cholesterol, and triglycerides in a cognitively normal aging Han Chinese population. Clinical interventions in aging. 2014; 9:1063–7. [PubMed: 25031531]
2. Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. International journal of cancer Journal international du cancer. 2008; 123:1693–8. [PubMed: 18646186]
3. Grant WB. A multicountry ecological study of risk-modifying factors for prostate cancer: apolipoprotein E epsilon4 as a risk factor and cereals as a risk reduction factor. Anticancer research. 2010; 30:189–99. [PubMed: 20150635]
4. Lehrer S. Possible relationship of the apolipoprotein E (ApoE) epsilon4 allele to prostate cancer. British journal of cancer. 1998; 78:1398. [PubMed: 9823988]
5. Niemi M, Kervinen K, Kiviniemi H, Lukkarinen O, Kyllonen AP, Apaja-Sarkkinen M, et al. Apolipoprotein E phenotype, cholesterol and breast and prostate cancer. Journal of epidemiology and community health. 2000; 54:938–9. [PubMed: 11076992]
6. Wessel N, Liestol K, Maehlen J, Brorson SH. The apolipoprotein E epsilon4 allele is no risk factor for prostate cancer in the Norwegian population. British journal of cancer. 2001; 85:1418. [PubMed: 11720484]
7. Shui IM, Mucci LA, Kraft P, Tamimi RM, Lindstrom S, Penney KL, et al. Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: a prospective nested case-control study. Journal of the National Cancer Institute. 2012; 104:690–9. [PubMed: 22499501]
8. Ifere GO, Desmond R, Demark-Wahnefried W, Nagy TR. Apolipoprotein E gene polymorphism influences aggressive behavior in prostate cancer cells by deregulating cholesterol homeostasis. International journal of oncology. 2013; 43:1002–10. [PubMed: 23934233]

Table 1

Odds ratio[1] of prostate cancer by apolipoprotein E genotype, Health Professionals Follow-up Study.

Prostate cancer	Apolipoprotein E genotype		
	e3e3	e2e2/e2e3	e4e4/e3e4
Total			
No.cases/controls	704/767	184/170	281/296
OR (95%CI)	1.00(Reference)	1.17(0.92–1.48)	1.05(0.86–1.27)
Gleason sum ≤ 7(3+4)			
No.cases/controls	545/767	144/170	211/296
OR (95%CI)	1.00(Reference)	1.17(0.91–1.51)	1.01(0.82–1.25)
Gleason sum ≥ 7(4+3)			
No.cases/controls	103/767	27/170	54/296
OR (95%CI)	1.00(Reference)	1.17(0.74–1.85)	1.38(0.96–1.97)
Clinically localized[2]			
No.cases/controls	564/767	150/170	232/296
OR (95%CI)	1.00(Reference)	1.19(0.93–1.53)	1.08(0.88–1.33)
Lethal[2]			
No.cases/controls	73/767	15/170	24/296
OR (95%CI)	1.00(Reference)	0.98(0.54–1.77)	0.87(0.53–1.42)

[1] Estimated from an unconditional logistic regression model, and adjusted for age at blood draw and time since blood draw to diagnosis.

[2] Clinically 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[1] of apolipoprotein E genotype with the risk of prostate cancer, stratified by circulating cholesterol concentration[2] and use of cholesterol-lowering drugs prior to diagnosis[3], Health Professionals Follow-up Study.

Outcome	Apolipoprotein E genotype					
	e3e3		e2e2/e2e3		e4e4/e3e4	
	No.cases/controls	OR (95%CI)	No.cases/controls	OR (95%CI)	No.cases/Controls	OR (95%CI)
Circulating cholesterol concentration						
Total						
< Median	355/377	1.00(Reference)	114/100	1.23(0.90–1.68)	131/136	1.06(0.79–1.41)
≥ Median	343/385	1.00(Reference)	68/69	1.05(0.73–1.52)	150/154	1.08(0.82–1.41)
Gleason sum ≤ 7(3+4)						
< Median	277/377	1.00(Reference)	90/100	1.22(0.88–1.70)	99/136	1.02(0.75–1.39)
≥ Median	262/385	1.00(Reference)	52/69	1.06(0.71–1.57)	112/154	1.05(0.78–1.40)
Gleason sum ≥ 7(4+3)						
< Median	47/377	1.00(Reference)	15/100	1.30(0.69–2.44)	22/136	1.31(0.76–2.28)
≥ Median	56/385	1.00(Reference)	12/69	1.11(0.57–2.19)	32/154	1.45(0.90–2.33)
Clinically Localized[4]						
< Median	282/377	1.00(Reference)	92/100	1.25(0.90–1.73)	107/136	1.09(0.80–1.47)
≥ Median	276/385	1.00(Reference)	56/69	1.09(0.74–1.60)	125/154	1.12(0.84–1.50)
Lethal[4]						
< Median	34/377	1.00(Reference)	9/100	1.19(0.54–2.64)	13/136	1.04(0.52–2.08)
≥ Median	39/385	1.00(Reference)	6/69	0.79(0.32–1.96)	11/154	0.72(0.36–1.46)
Use of cholesterol-lowering drugs prior to diagnosis						
Total						
Never	497/492	1.00(Reference)	153/126	1.23(0.94–1.60)	196/178	1.09(0.86–1.38)
Ever	207/229	1.00(Reference)	31/37	0.93(0.55–1.55)	85/97	0.97(0.69–1.38)
Gleason sum ≤ 7(3+4)						
Never	379/492	1.00(Reference)	122/126	1.28(0.96–1.70)	151/178	1.10(0.85–1.42)
Ever	166/229	1.00(Reference)	22/37	0.82(0.47–1.45)	60/97	0.85(0.58–1.25)
Gleason sum ≥ 7(4+3)						

Outcome	Apolipoprotein E genotype					
	e3e3		e2e2/e2e3		e4e4/e3e4	
	No.cases/controls	OR (95%CI)	No.cases/controls	OR (95%CI)	No.cases/Controls	OR (95%CI)
Never	76/492	1.00(Reference)	19/126	1.00(0.58–1.72)	34/178	1.24(0.80–1.92)
Ever	27/229	1.00(Reference)	8/37	1.76(0.74–4.20)	20/97	1.79(0.95–3.35)
Clinically Localized[4]						
Never	393/492	1.00(Reference)	124/126	1.26(0.95–1.67)	162/178	1.14(0.89–1.47)
Ever	171/229	1.00(Reference)	26/37	0.94(0.55–1.62)	70/97	0.97(0.68–1.41)
Lethal[4]						
Never	63/492	1.00(Reference)	13/126	0.89(0.47–1.70)	20/178	0.88(0.51–1.52)
Ever	10/229	1.00(Reference)	2/37	1.25(0.26–5.97)	4/97	0.93(0.28–3.06)

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

[2] Cholesterol 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 and 2004: 202.0 mg/dL.

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

[4] Clinically 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.