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

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# 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.

Disclosure of Potential Conflicts of Interest

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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,

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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 E4 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 multicountry 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.

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#### Table 1

Odds ratio<sup>1</sup> of prostate cancer by apolipoprotein E genotype, Health Professionals Follow-up Study.

Prostate cancer	Apolipoprotein I	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	i+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	12		
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 <sup>2</sup>			
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)

 $^{I}$ Estimated from an unconditional logistic regression model, and adjusted for age at blood draw and time since blood draw to diagnosis.

<sup>2</sup>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<sup>1</sup> of apolipoprotein E genotype with the risk of prostate cancer, stratified by circulating cholesterol concentration<sup>2</sup> and use of cholesterollowering drugs prior to diagnosis<sup>3</sup>, Health Professionals Follow-up Study.

Outcome $e3-3$ $e3-3$ $e3-3$ $e4-4e3-6$ $e4-4e3-6$ $OR$ No.cases/controlsOR (95%CT)No.cases/controlsOR (95%CT)No.cases/controlsORCirculating cholesterol concentration $335377$ $1000$ $12300-1.68$ $131/135$ $100$ Circulating $335377$ $1000R$ eference $8869$ $114/100$ $12300-1.68$ $131/135$ $100$ Media $337377$ $1000R$ eference $8869$ $105073-1.52$ $150/154$ $100$ Media $277377$ $1000R$ eference $90/100$ $122008-1.73$ $100$ $100$ Media $277377$ $1000R$ eference $5569$ $11006071-1.57$ $112154$ $100$ Media $277377$ $1000R$ eference $157100$ $120069-2.44$ $22136$ $1.44$ Media $26335$ $1.000R$ eference $157100$ $130(69-2.44)$ $27144$ $1.47$ Media $276385$ $1.000R$ eference $1269$ $1.11(057-2.19)$ $127164$ $1.41$ Media $282377$ $1.000R$ eference $2509$ $1.100607-1.56$ $127164$ $1.41$ Media $282377$ $1.000R$ eference $2509$ $1.0000-1.75$ $1.41$ $1.41$ Media $282377$ $1.000R$ eference $2509$ $1.0000-1.75$ $1.000$ $1.21$ Media $27354$ $1.000R$ eference $2509$ $1.0000-1.75$ $1.000$ $1.0000$ Media $282377$ $1.000R$ eference $2509$ $1.0000-1.75$ $1.000R$ $1.000R$ Media <th></th> <th>Apolipoprotein E genotype</th> <th>genotype</th> <th></th> <th></th> <th></th> <th></th>		Apolipoprotein E genotype	genotype				
95%CT)         No.cases/controls         OR (95%CT)         No.cases/controls           87%CT)         114/100         1.23(0.90-1.68)         131/136           Reference)         68/69         1.05(0.73-1.52)         150/154           Reference)         90/100         1.23(0.90-1.68)         131/136           Reference)         90/100         1.23(0.90-1.57)         150/154           Reference)         52/69         1.06(0.71-1.57)         112/154           Reference)         15/100         1.30(0.69-2.44)         22/136           Reference)         12/69         1.10(0.57-2.19)         32/154           Reference)         92/100         1.30(0.69-2.44)         22/136           Reference)         92/100         1.30(0.69-2.44)         22/136           Reference)         56/69         1.09(0.74-1.60)         12/154           Reference)         56/69         0.79(0.32-1.96)         11/154           Reference)         6/69         0.79(0.32-1.96)         11/154           Reference)         153/126         12/136         11/154           Reference)         153/126         12/136         11/154           Reference)         153/126         12/106         12/178	Outcome	<u>e</u> 3e3		<u>e2e2/e2e3</u>		<u>e4e4/e3e4</u>	
Reference)       114/100       1.23(0.90-1.68)       131/136         Reference)       68/69       1.05(0.73-1.52)       150/154         Reference)       90/100       1.22(0.88-1.70)       99/136         Reference)       52/69       1.06(0.71-1.57)       112/154         Reference)       15/100       1.30(0.69-2.44)       22/136         Reference)       12/69       1.11(0.57-2.19)       32/154         Reference)       12/69       1.11(0.57-2.19)       32/154         Reference)       92/100       1.25(0.90-1.73)       107/136         Reference)       92/100       1.19(0.54-2.64)       13/136         Reference)       6/69       0.79(0.32-1.96)       11/154         Reference)       6/69       0.79(0.32-1.96)       11/154         Reference)       13/136       11/154       1         Reference)       31/37       0.33(0.55-1.55)       85/97         Reference)       31/37       0.93(0.55-1.55)       85/97         Reference)       122/126       1.28(0.96-1.70)       196/178         Reference)       21/37       0.93(0.55-1.55)       85/97         Reference)       22/126       1.28(0.96-1.70)       196/178		No.cases/controls	OR (95%CI)	No.cases/controls	OR (95%CI)	No.cases/Controls	OR (95%CI)
an $355/377$ $1.00$ (Reference) $114/100$ $1.230.90-1.68$ $131/136$ an $343.385$ $1.00$ (Reference) $68.69$ $1.05(0.73-1.52)$ $150/154$ ansun $7(3+4)$ $1.00$ (Reference) $68.69$ $1.05(0.73-1.52)$ $150/154$ ansun $7(3+4)$ $1.00$ (Reference) $5269$ $1.05(0.71-1.57)$ $112/154$ an $47/377$ $1.00$ (Reference) $5269$ $1.060.71-1.57)$ $112/154$ an $47/377$ $1.00$ (Reference) $57/100$ $1.300.69-2.44$ $22/136$ an $47/377$ $1.00$ (Reference) $57/100$ $1.300.69-2.44$ $22/136$ an $56/385$ $1.00$ (Reference) $56/9$ $1.11(0.57-2.19)$ $32/154$ an $2376/385$ $1.00$ (Reference) $56/9$ $1.00(0.74-1.60)$ $127/136$ an $2376/385$ $1.00$ (Reference) $56/9$ $1.000(0.74-1.60)$ $127/136$ an $2376/385$ $1.00$ (Reference) $56/9$ $1.090.74-1.60$ $137/36$ an $2376/385$ $1.00$ (Reference)	Circulatin	g cholesterol concent	ration				
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init       343385       1.00(Reference)       68/69       1.05(0.73-1.52)       150/154         init       7(3+4)       90/100       1.22(0.88-1.70)       9/136         init       262385       1.00(Reference)       50/100       1.22(0.88-1.70)       9/136         init       262385       1.00(Reference)       50/100       1.22(0.88-1.70)       9/136         init       262385       1.00(Reference)       50/69       1.00(Reference)       12/105       12/154         init       56/385       1.00(Reference)       12/100       1.20(0.69-2.44)       22/136         init       56/385       1.00(Reference)       20/100       1.20(0.69-2.44)       22/136         init       282/377       1.00(Reference)       20/100       1.20(0.69-2.44)       22/136         init       282/377       1.00(Reference)       56/69       1.00(Reference)       20/136       1.01/136         init       282/377       1.00(Reference)       56/69       1.00(Reference)       21/100       1.21/136         init       382/377       1.00(Reference)       56/69       1.00(Reference)       21/100       1.21/136         init       382/37       1.00(Reference)       6/100       1.21/00	< Median		1.00(Reference)	114/100	1.23(0.90 - 1.68)	131/136	1.06(0.79 - 1.41)
In         7(3+4)         7(3+4)         9(136)           In         277/377         1.00(Reference)         9(100)         1.22(0.88-1.70)         9(136)           In         277/377         1.00(Reference)         52/69         1.06(0.71-1.57)         112/154           In         47/377         1.00(Reference)         52/69         1.06(0.71-1.57)         112/154           In         47/377         1.00(Reference)         52/69         1.00(Reference)         22/136           In         282/377         1.00(Reference)         22/100         1.25(0.90-1.73)         107/136           In         282/377         1.00(Reference)         56/69         1.09(0.74-1.60)         12/136           In         276/385         1.00(Reference)         56/69         1.99(0.74-1.60)         12/136           In         34/377         1.00(Reference)         56/69         1.99(0.74-1.60)         12/136           In         34/377         1.00(Reference)         56/69         1.99(0.74-1.60)         12/136           In         34/377         1.00(Reference)         56/69         0.79(0.32-1.96)         11/154           In         34/377         1.00(Reference)         56/69         0.79(0.32-1.96)         11/154 </td <td>Median</td> <td></td> <td>1.00(Reference)</td> <td>68/69</td> <td>1.05(0.73-1.52)</td> <td>150/154</td> <td>1.08(0.82-1.41)</td>	Median		1.00(Reference)	68/69	1.05(0.73-1.52)	150/154	1.08(0.82-1.41)
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int       262/385       1.00(Reference)       52/69       1.06(0.71-1.57)       112/154         int       7(4+3)       1.00(Reference)       15/100       1.30(0.69-2.44)       22/136         int       56/385       1.00(Reference)       12/100       1.30(0.69-2.44)       22/136         int       26/385       1.00(Reference)       12/100       1.30(0.69-2.44)       22/136         int       282/377       1.00(Reference)       92/100       1.26(0.90-1.73)       107/136         int       282/377       1.00(Reference)       92/100       1.26(0.90-1.73)       107/136         int       282/377       1.00(Reference)       92/100       1.26(0.90-1.73)       107/136         int       34/377       1.00(Reference)       92/100       1.26(0.90-1.73)       107/136         int       34/377       1.00(Reference)       97/100       1.26(0.90-1.76)       13/136         int       33/335       1.00(Reference)       96/97       0.79(0.32-1.56)       85/97         int       33/335       1.00(Reference)       31/37       0.93(0.55-1.55)       85/97         int       37/492       1.00(Reference)       31/37       0.93(0.55-1.55)       85/97         int       1	< Median	277/377	1.00(Reference)	90/100	1.22(0.88–1.70)	99/136	1.02(0.75-1.39)
m sum $7(4+3)$ ian $47/377$ $1.00(\text{Reference})$ $15/100$ $1.30(0.69-2.44)$ $22/136$ ian $56/385$ $1.00(\text{Reference})$ $12/69$ $1.11(0.57-2.19)$ $32/154$ ian $282/377$ $1.00(\text{Reference})$ $92/100$ $1.25(0.90-1.73)$ $107/136$ ian $282/377$ $1.00(\text{Reference})$ $56/69$ $1.09(0.74-1.60)$ $125/154$ ian $23/377$ $1.00(\text{Reference})$ $56/69$ $1.09(0.74-1.60)$ $125/154$ $4$ $4$ $1.00(\text{Reference})$ $56/69$ $1.09(0.74-1.60)$ $12/136$ ian $34/377$ $1.00(\text{Reference})$ $56/69$ $1.09(0.74-1.60)$ $13/136$ ian $34/377$ $1.00(\text{Reference})$ $6/69$ $0.79(0.32-1.96)$ $11/154$ ian $39/385$ $1.00(\text{Reference})$ $56/97$ $0.79(0.32-1.56)$ $85/97$ ian $39/385$ $1.00(\text{Reference})$ $153/126$ $0.79(0.32-1.56)$ $85/97$ ian $37/449$ $1.00($	Median		1.00(Reference)	52/69	1.06(0.71 - 1.57)	112/154	1.05(0.78 - 1.40)
and       47/377       1.00(Reference)       15/100       1.30(0.69-2.44)       22/136         and       56/385       1.00(Reference)       12/69       1.11(0.57-2.19)       32/154         and       282/377       1.00(Reference)       92/100       1.25(0.90-1.73)       107/136         and       282/377       1.00(Reference)       56/69       1.09(0.74-1.60)       125/154         and       282/377       1.00(Reference)       56/69       1.09(0.74-1.60)       125/154         and       34/377       1.00(Reference)       6/69       0.79(0.32-1.96)       11/154         d       39/385       1.00(Reference)       6/69       0.79(0.32-1.96)       11/154         d       39/385       1.00(Reference)       153/126       1.23(0.94-1.60)       196/178         ian       39/385       1.00(Reference)       153/126       1.23(0.94-1.60)       196/178         aim       70+43       0.00(Reference)       153/126       1.23(0.94-1.60)       196/178         ian       39/385       1.00(Reference)       31/37       0.93(0.55-1.55)       85/97         ian       379/492       1.00(Reference)       22/37       0.82(0.47-1.45)       0.97/178         ian       70+	Gleason st	um 7(4+3)					
iai 56/385 1.00(Reference) 12/69 1.11(0.57–2.19) 32/154 <b>Illy Localized<sup>4</sup></b> iai 282/377 1.00(Reference) 92/100 1.25(0.90–1.73) 107/136 iai 23/37 1.00(Reference) 56/69 1.09(0.74–1.60) 125/154 4 iai 34/377 1.00(Reference) 6/69 0.79(0.32–1.96) 11/154 iai 39/385 1.00(Reference) 6/69 0.79(0.32–1.96) 11/154 iai 39/385 1.00(Reference) 6/69 0.79(0.32–1.96) 11/154 cholesterol-lowering drugs prior to diagnosis cholesterol-lowering drugs prior to diagnosis 497/492 1.00(Reference) 153/126 1.23(0.94–1.60) 196/178 497/492 1.00(Reference) 153/126 1.23(0.94–1.60) 196/178 7(3+4) 379/492 1.00(Reference) 122/126 1.23(0.94–1.60) 196/178 379/492 1.00(Reference) 22/37 0.93(0.55–1.55) 85/97 an sum 7(3+4) 7(3+4) 1.00(Reference) 22/37 0.82(0.47–1.45) 60/97 an 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)
III Localized <sup>4</sup> ian $282377$ $1.00(\text{Reference})$ $92/100$ $1.25(0.90-1.73)$ $107/136$ ian $276/385$ $1.00(\text{Reference})$ $56/69$ $1.09(0.74-1.60)$ $125/154$ $4$ $34377$ $1.00(\text{Reference})$ $9/100$ $1.19(0.54-2.64)$ $13/136$ ian $34377$ $1.00(\text{Reference})$ $6/69$ $0.79(0.32-1.96)$ $11/154$ ian $39/385$ $1.00(\text{Reference})$ $6/69$ $0.79(0.32-1.96)$ $11/154$ cholesterol-lowering drugs prior to diagnosis $1.23(0.94-1.60)$ $196/178$ $100(\text{Reference})$ $31/37$ $0.39(0.55-1.55)$ $85/97$ an sum $7(3+4)$ $1.00(\text{Reference})$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $379/492$ $1.00(\text{Reference})$ $31/37$ $0.33(0.55-1.55)$ $85/97$ $379/492$ $1.00(\text{Reference})$ $22/37$ $0.32(0.47-1.45)$ $6097$ $379/492$ $1.00(\text{Reference})$ $22/37$ $0.82(0.47-1.45)$ $6097$	Median	56/385	1.00(Reference)	12/69	1.11(0.57–2.19)	32/154	1.45(0.90-2.33)
in       282/377       1.00(Reference)       92/100       1.25(0.90-1.73)       107/136         in $276/385$ $1.00(Reference)$ $56/69$ $1.09(0.74-1.60)$ $125/154$ d $34/377$ $1.00(Reference)$ $9/100$ $1.19(0.54-2.64)$ $13/136$ in $39/385$ $1.00(Reference)$ $6/69$ $0.79(0.32-1.96)$ $11/154$ in $39/385$ $1.00(Reference)$ $6/69$ $0.79(0.32-1.96)$ $11/154$ cholesterol-lowering drugs prior to diagnosis $1.00(Reference)$ $5/737$ $0.79(0.32-1.96)$ $11/154$ $497/492$ $1.00(Reference)$ $31/37$ $0.33(0.55-1.56)$ $85/97$ an sum $7(3+4)$ $1.200(Reference)$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $707/229$ $1.00(Reference)$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $8 sum$ $7(3+4)$ $1.00(Reference)$ $31/37$ $0.93(0.55-1.56)$ $85/97$ $707/229$ $1.00(Reference)$ $31/37$ $0.93(0.55-1.56)$ $85/97$ $8 sum$ $7(3+3)$ $0.93(0.55-1.56)$ $85/97$ $86/97$	Clinically	Localized <sup>4</sup>					
im276/3851.00(Reference) $56/69$ 1.09(0.74–1.60) $125/154$ $t$ $34/377$ $1.00(Reference)$ $9/100$ $1.19(0.54–2.64)$ $13/136$ im $34/377$ $1.00(Reference)$ $6/69$ $0.79(0.32–1.96)$ $11/154$ im $39/385$ $1.00(Reference)$ $6/69$ $0.79(0.32–1.96)$ $11/154$ cholesterol-lowering drugs prior to diagnosis497/492 $1.00(Reference)$ $153/126$ $1.23(0.94-1.60)$ $196/178$ 207/229 $1.00(Reference)$ $31/37$ $0.93(0.55-1.55)$ $85/97$ an sum $7(3+4)$ $7(3+4)$ $7(3+4)$ $1.22/126$ $1.28(0.96-1.70)$ $151/178$ $166/229$ $1.00(Reference)$ $22/37$ $0.82(0.47-1.45)$ $60/97$ an sum $7(4+3)$	< Median	282/377	1.00(Reference)	92/100	1.25(0.90 - 1.73)	107/136	1.09(0.80 - 1.47)
4         ian $34/377$ $1.00(\text{Reference})$ $9/100$ $1.19(0.54-2.64)$ $13/136$ ian $39/385$ $1.00(\text{Reference})$ $6/69$ $0.79(0.32-1.96)$ $11/154$ cholesterol-lowering drugs prior to diagnosis $0.79(0.32-1.96)$ $11/154$ $497/492$ $1.00(\text{Reference})$ $55/126$ $1.23(0.94-1.60)$ $96/178$ $207/229$ $1.00(\text{Reference})$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $n sum$ $7(3+4)$ $0.93(0.55-1.56)$ $85/97$	Median	276/385	1.00(Reference)	56/69	1.09(0.74 - 1.60)	125/154	1.12(0.84 - 1.50)
ian $34/377$ $1.00(\text{Reference})$ $9/100$ $1.19(0.54-2.64)$ $13/136$ ian $39/385$ $1.00(\text{Reference})$ $6/69$ $0.79(0.32-1.96)$ $11/154$ cholesterol-lowering drugs prior to diagnosis $1.00(\text{Reference})$ $5/69$ $0.79(0.32-1.96)$ $11/154$ etholesterol-lowering drugs prior to diagnosis $1.00(\text{Reference})$ $153/126$ $1.23(0.94-1.60)$ $196/178$ $497/492$ $1.00(\text{Reference})$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $ansum$ $7(3+4)$ $1.00(\text{Reference})$ $31/37$ $0.93(0.55-1.55)$ $85/97$ $379/492$ $1.00(\text{Reference})$ $122/126$ $1.28(0.96-1.70)$ $151/178$ $379/492$ $1.00(\text{Reference})$ $22/37$ $0.82(0.47-1.45)$ $60/97$ $166/229$ $1.00(\text{Reference})$ $22/37$ $0.82(0.47-1.45)$ $60/97$	Lethal <sup>4</sup>						
ian     39/385     1.00(Reference)     6/69     0.79(0.32-1.96)     11/154       cholesterol-lowering drugs prior to diagnosis     497/492     1.00(Reference)     153/126     1.23(0.94-1.60)     196/178       497/492     1.00(Reference)     31/37     0.93(0.55-1.55)     85/97       an sum     7(3+4)     1.00(Reference)     31/37     0.93(0.55-1.55)     85/97       57/229     1.00(Reference)     31/37     0.93(0.55-1.55)     85/97       an sum     7(3+4)     1.22/126     1.28(0.96-1.70)     151/178       166/229     1.00(Reference)     22/37     0.82(0.47-1.45)     60/97       an sum     7(4+3)     0.82(0.47-1.45)     60/97	< Median	34/377	1.00(Reference)	9/100	1.19(0.54-2.64)	13/136	1.04(0.52-2.08)
cholesterol-lowering drugs prior to diagnosis         497/492       1.00(Reference)       153/126       1.23(0.94-1.60)       196/178         207/229       1.00(Reference)       31/37       0.93(0.55-1.55)       85/97         an sum       7(3+4)       0.93(0.55-1.55)       85/97         379/492       1.00(Reference)       122/126       1.28(0.96-1.70)       151/178         166/229       1.00(Reference)       22/37       0.82(0.47-1.45)       60/97         an sum       7(4+3)       0.82(0.47-1.45)       60/97	Median	39/385	1.00(Reference)	6/9	0.79(0.32–1.96)	11/154	0.72(0.36–1.46)
497/492       1.00(Reference)       153/126       1.23(0.94–1.60)       196/178         207/229       1.00(Reference)       31/37       0.93(0.55–1.55)       85/97 <b>n sum 7(3+4)</b> 0.93(0.55–1.55)       85/97         379/492       1.00(Reference)       122/126       1.28(0.96–1.70)       151/178         166/229       1.00(Reference)       22/37       0.82(0.47–1.45)       60/97	Use of cho	lesterol-lowering dru	igs prior to diagnoe	sis			
497/492     1.00(Reference)     153/126     1.23(0.94-1.60)     196/178       207/229     1.00(Reference)     31/37     0.93(0.55-1.55)     85/97       n sum     7(3+4)     1.00(Reference)     122/126     1.28(0.96-1.70)     151/178       379/492     1.00(Reference)     22/37     0.82(0.47-1.45)     60/97       n sum     7(4+3)	Total						
207/229     1.00(Reference)     31/37     0.93(0.55-1.55)     85/97 <b>n sum</b> 7(3+4)	Never	497/492	1.00(Reference)	153/126	1.23(0.94 - 1.60)	196/178	1.09(0.86 - 1.38)
n sum 7(3+4) 379/492 1.00(Reference) 122/126 1.28(0.96–1.70) 151/178 166/229 1.00(Reference) 22/37 0.82(0.47–1.45) 60/97 nn sum 7(4+3)	Ever	207/229	1.00(Reference)	31/37	0.93(0.55–1.55)	85/97	0.97(0.69–1.38)
379/492         1.00(Reference)         122/126         1.28(0.96-1.70)         151/178           166/229         1.00(Reference)         22/37         0.82(0.47-1.45)         60/97 <b>n sum</b> 7(4+3)         1.00(Reference)         22/37         0.82(0.47-1.45)         60/97	Gleason st	111 <b>7</b> (3+4)					
1.00(Reference) 22/37 0.82(0.47–1.45) 60/97	Never	379/492	1.00(Reference)	122/126	1.28(0.96 - 1.70)	151/178	1.10(0.85-1.42)
Gleason sum 7(4+3)	Ever	166/229	1.00(Reference)	22/37	0.82(0.47–1.45)	60/97	0.85(0.58 - 1.25)
	Gleason st	um 7(4+3)					

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Outcome	e3e3		e2e2/e2e3		e4e4/e3e4	
	No.cases/controls OR (95%CI)	OR (95%CI)	No.cases/controls OR (95%CI)	OR (95%CI)	No.cases/Controls OR (95%CI)	OR (95%CI)
Never	76/492	1.00(Reference) 19/126	19/126	1.00(0.58–1.72) 34/178	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	Clinically Localized <sup>4</sup>					
Never	393/492	1.00(Reference) 124/126	124/126	1.26(0.95–1.67) 162/178	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 <sup>4</sup>						
Never	63/492	1.00(Reference) 13/126	13/126	0.89(0.47–1.70) 20/178	20/178	0.88(0.51 - 1.52)
Ever	10/229	1.00(Reference) 2/37	2/37	1.25(0.26–5.97) 4/97	4/97	0.93(0.28 - 3.06)

164.4 mg/dL and 2004: 202.0 mg/dL.

 ${}^{\mathcal{J}}_{\mathcal{P}}$  reontrols, using the diagnosed date of their matched cases.

<sup>4</sup> 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.