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PRINCIPAL INVESTIGATOR: Wildon Farwell

CONTRACTING ORGANIZATION: Brigham and Women's Hospital, Inc.
Boston, MA 02115

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The Relationship between Statins and Prostate Cancer Prevention

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6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Brigham and Women's Hospital, Inc.
Boston, MA 02115

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14. ABSTRACT
Prostate cancer is the most frequently diagnosed cancer among men in the United States, excluding non-melanoma skin cancer. Few risk factors and prevention strategies for prostate cancer are known. Some evidence suggests that statins, a class of medications that lower cholesterol, may reduce the incidence and progression of prostate cancer. Dr. Farwell obtained training that allowed him to investigate the relationship between statins and prostate cancer incidence and progression. He took classes at the Harvard School of Public Health and had regular research meetings with researchers at the Brigham and Women's Hospital and the VA Boston Healthcare System. He assembled datasets and performed analyses that examined the relationship between statins and total prostate cancer incidence as well as the incidence of both low and high grade prostate cancer.

15. SUBJECT TERMS
prostate cancer; statins; epidemiology

16. SECURITY CLASSIFICATION OF:
a. REPORT | U
b. ABSTRACT | U
c. THIS PAGE | U

17. LIMITATION OF ABSTRACT | UU
18. NUMBER OF PAGES | 40

19a. NAME OF RESPONSIBLE PERSON
USAMRMC
19b. TELEPHONE NUMBER (include area code)
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</tbody>
</table>
Introduction

Prostate cancer is the most frequently diagnosed cancer, excluding non-melanoma skin cancer, in the United States. In 2011, it is estimated that 240,890 men will be diagnosed with prostate cancer and 33,720 men will die from prostate cancer. Few prevention strategies for prostate cancer exist. HMG-CoA reductase inhibitors, statins, may prevent prostate cancer incidence and progression. We previously reported that statin users were 10% less likely to develop any prostate cancer compared to users of anti-hypertensive medications. Other papers have reported that statin users are at decreased risk for any prostate cancer. However, these studies have primarily investigated the general relationship between statin use and total prostate cancer incidence and not the specific relationship between statin use and the grade of prostate cancer at diagnosis or prostate cancer progression. Therefore, we performed sophisticated analyses and I obtained additional training at the Harvard School of Public Health that enabled me to examine the specific relationship between statins and prostate cancer among men with various levels of risk for prostate cancer. Our studies will investigated the relationship between statin use and prostate cancer grade at diagnosis and prostate cancer progression using data from the Physicians’ Health Study and VA New England Healthcare System.

Body

I met regularly with researchers at both Brigham and Women’s Hospital and the VA Boston Healthcare System. I met regularly with my primary mentor, J. Michael Gaziano, MD MPH. During these meetings, Dr. Gaziano and I discussed current research findings and opportunities for new research. We also attend regular research meetings at the VA Boston Healthcare System. At these research meetings, current research projects in the VA Healthcare System were discussed. I strengthened my research ties with the Massachusetts Veterans Epidemiology Research and Information Center at the VA Boston Healthcare System. I worked with several investigators such as Drs. Leonard D’Avolio, PhD, and Elizabeth V. Lawler, ScD MPH, on projects related to prostate cancer incidence and progression.

I performed analyses of data from the Physicians’ Health Study (PHS) II, Appendix 2. In brief, I examined the relationship between ever taking a cholesterol lowering medication and the incidence of prostate cancer. I also examined the relationship between cholesterol and prostate cancer incidence. In both analyses, I attempted to control for multiple confounders including comorbid conditions. After performing multiple analyses, I was not able to find a convincing relationship between statins and prostate cancer incidence. The p-value for a hazard ratio for a history of cholesterol lowering medication use and current cholesterol medication use was 0.16 and 0.56, respectively. I was also not able to find a convincing relationship between cholesterol and prostate cancer incidence. The p-value for a test of trend across quartiles of cholesterol was 0.9062. Because these results were inconclusive, we have decided not to publish our findings at this time.

I published my findings from the VA New England Healthcare System, Appendix 3. In brief, I used electronic and administrative files to identify 55,875 men who were either taking a statin or antihypertensive medication and were routine users of the VA New England Healthcare System. I then created age- and multivariate-adjusted Cox proportional hazard models to calculate the hazard ratio (HR), 95% confidence interval (CI), for prostate cancer incidence among patients taking statins compared to patients taking antihypertensive medications. I also grouped patients taking statins into categories of equivalent simvastatin dosages and then compared these groups to patients taking antihypertensive medications for the incidence of prostate cancer. Furthermore, I performed similar
analyses examining the relationship between using statins compared to antihypertensive medications for the incidence of low-grade and high-grade prostate cancer. Low-grade prostate cancer was defined as a Gleason score of $\leq 7$ (3+4) at biopsy and high-grade prostate cancer was defined as a Gleason score of $\geq 7$ (4+3) at biopsy.

Compared to men taking an antihypertensive medication, men taking a statin were 30% less likely to be diagnosed with prostate cancer, Table 2. Furthermore, statin users were 13% less likely to be diagnosed with low-grade prostate cancer but 60% less likely to be diagnosed with high-grade prostate cancer. A dose response for prostate cancer incidence was also identified with an increased dose of statin associated with a decreased risk for prostate cancer and high-grade prostate cancer. A paper describing these results was published in the *Journal of the National Cancer Institute*.

Table 2. Multivariate * adjusted hazard ratios (95% confidence interval) for total prostate cancer, low grade prostate cancer, and high grade prostate cancer by statin use and categories of equivalent simvastatin doses.

<table>
<thead>
<tr>
<th>Categories of Equivalent Simvastatin Doses</th>
<th>Statin 0 mg</th>
<th>1-10 mg</th>
<th>11 – 19 mg</th>
<th>$\geq$ 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>0.70 (0.53, 0.91)</td>
<td>Referent</td>
<td>0.68 (0.52, 0.91)</td>
<td>0.68 (0.50, 0.92)</td>
</tr>
<tr>
<td>Gleason Score $\leq 7$ (3+4)</td>
<td>0.87 (0.63, 1.21)</td>
<td>Referent</td>
<td>0.82 (0.59, 1.13)</td>
<td>0.78 (0.55, 1.12)</td>
</tr>
<tr>
<td>Gleason Score $\geq 7$ (4+3)</td>
<td>0.40 (0.25, 0.65)</td>
<td>Referent</td>
<td>0.43 (0.25, 0.74)</td>
<td>0.48 (0.27, 0.87)</td>
</tr>
</tbody>
</table>

* Multivariate adjusted models were adjusted for the following variables: statin use (yes, no), finasteride use history (yes, no), age (years), serum total cholesterol (mg/dL), race (white, black, other, missing), smoking history (yes, no), aspirin use (yes, no), heart disease (yes, no), diabetes mellitus (yes, no), history of PSA test (yes, no)

I am awaiting additional mortality data to complete this analysis in the Early Stage Prostate Cancer Cohort on the relationship between statin use and mortality among men diagnosed with early stage prostate cancer. My preliminary analyses to date indicate that statins may be associated with decreased risk for prostate cancer related mortality among men who are diagnosed with early stage prostate cancer.

In addition, I also published on the relationship between height and prostate cancer grade among men diagnosed with early stage prostate cancer, Appendix 4. In brief, I performed logistic regression to calculate the odds ratio (OR), 95% confidence interval (CI), for the association between height and prostate cancer grade at diagnosis. I found that taller men were more likely to be diagnosed with high
grade prostate cancer, OR 1.11 (95% CI 0.96, 1.29). In addition, taller diabetic men, OR 1.35 (95% CI 1.00, 1.81), and African-American men, OR 1.44 (95% CI 1.06, 1.95), were particularly more likely to be diagnosed with high grade prostate cancer. A paper describing these results has been published in Cancer Causes and Control.

Key Research Accomplishments

a) Paper published in the Journal of the National Cancer Institute describing the results of the analysis in the New England Healthcare System. We found that statin use was associated with a 30% risk reduction in prostate cancer and a 13% risk reduction in low-grade prostate cancer and 60% risk reduction in high-grade prostate cancer.

b) Paper published in Cancer Causes and Control describing the results of an analysis in the Early Stage Prostate Cancer Cohort. We found that height was associated with high-grade prostate cancer. In particular, taller diabetic men and African-American men were particularly more likely to be diagnosed with high-grade prostate cancer. Although this analysis was not outlined in my original statement of work, it is a related topic using a dataset described in my proposal.

c) Presented results from my analyses in the VA New England Healthcare System at IMPaCT in Orlando, FL, in March, 2011.

Reportable Outcomes

The third and final year of my research training award was dedicated to analyzing datasets from the Physicians’ Health Study and publishing results from datasets of the VA New England Healthcare System, and Early Stage Prostate Cancer Cohort Study. I presented an oral abstract and poster at IMPaCT from work I did with data from the VA New England Healthcare System.

Conclusion

During the third and final year of the Physician Research Training Award, I left full-time employment at the VA Boston Healthcare System and Brigham and Women’s Hospital and am now fully employed at Biogen Idec, a pharmaceutical company. However, I completed two manuscripts and published these in addition to continuing to explore the relationship between statins, cholesterol and prostate cancer in the Physicians’ Health Study and Early Stage Prostate Cancer Cohort study.

Prostate cancer is commonly diagnosed and prevention strategies for prostate cancer incidence and progression are needed. Statins may be a safe and effective treatment for prostate cancer prevention. I believe the results of my studies contributed to better understanding the risk factors for high-grade prostate cancer and a possible prevention strategy for high-grade prostate cancer. The training that I obtained during this grant will help me develop new treatments for multiple potential indications in my new role at a pharmaceutical company.
Appendix 1: CV of Dr. Wildon R. Farwell, MD MPH
Harvard Medical School/Harvard School of Dental Medicine  
Curriculum Vitae

Date Prepared: 11 September 2011

Name: Wildon R. Farwell, MD MPH

Office Address: VA Boston Healthcare System  
MAVERIC  
150 S. Huntington Avenue  
Boston, MA 02130

Brigham and Women’s Hospital  
Division of Aging  
1620 Tremont Street  
Boston, MA 02120

Home Address: 6 Glezen Lane  
Wayland, MA 01778

Work Phone: VA: 857-364-4201  
BWH: 617-278-0785

Work Email: VA: wildon.farwell@va.gov  
BWH: wfarwell@partners.org

Work FAX: VA: 857-364-4424  
BWH: 617-525-7739

Place of Birth: Springfield, MO; USA

Education

1996  BS Biology  University of Missouri- 
(Magna cum laude) Columbia, Columbia, MO

2000  MD Medicine  University of Missouri-
Columbia School of  
Medicine, Columbia, MO

2005  MPH Clinical Effectiveness  Harvard School of Public 
Health, Boston, MA

Postdoctoral Training

7/2000 - 6/2003  Resident Internal Medicine  Indiana University, 
Internal Medicine  Indianapolis, IN
7/2003 - 6/2006 Fellow General Internal Medicine Harvard Medical School, Boston, MA

**Faculty Academic Appointments**

2006 - 2010 Instructor Medicine Harvard Medical School, Boston, MA
2010 - Assistant Professor Medicine Harvard Medical School, Boston, MA

**Appointments at Hospitals/Affiliated Institutions**

- July, 2003 - 2007 Associate Physician Medicine (Aging) Brigham and Women’s Hospital, Boston, MA
- July, 2004 - 2007 Courtesy Medical Staff Medicine Faulkner Hospital, Boston, MA
- July, 2007 - Staff Physician Medicine (General Medicine) VA Boston Healthcare System, Boston, MA
- July, 2007 - Associate Epidemiologist Medicine (Aging) Brigham and Women’s Hospital, Boston, MA
- June, 2010 - Adjunct Instructor of Medicine Boston University School of Medicine, Boston, MA

**Major Administrative Leadership Positions**

- Local
  - 2007 - Associate Director, Harvard Medical School Fellowship in General Medicine and Primary Care at the VA Boston Healthcare System VA Boston Healthcare System, Boston, MA

**Committee Service**

- Local
  - 1998-2000 Admissions Committee, Member University of Missouri-Columbia, School of Medicine, Columbia, MO
  - 2007- Institutional Review Board, Member VA Boston Healthcare System, Boston, MA

- National and International
  - 2003-2005 Residency Review Committee for Internal Medicine, Member Accreditation Council for Graduate Medical Education
  - 2010- Executive Committee for CSP 572: Genetics of Functional Disability in Schizophrenia and Bipolar Illness VA Healthcare System
**Professional Societies**

2000- American College of Physicians  
2003 President, Indiana Council of Associates  
2002- Society of General Internal Medicine  
2005-2006 Member  
2006-2007 Member, National Meeting Programming Committee  
2007- Member, Abstract Review Committee  
2006-2007 Member, Finance Committee

**Editorial Activities**

Ad Hoc Reviewer, Archives of Internal Medicine  
European Journal of Epidemiology  
Clinical Endocrinology  
Diabetes Care

**Other Editorial Roles**

2009 - Editorial Board Open Journal of Oncology

**Honors and Prizes**

1997 Student Leadership and Service Award University of Missouri-Columbia, School of Medicine  
2000 Holt Leadership Award University of Missouri-Columbia, School of Medicine  
2000 Commencement Speaker University of Missouri-Columbia, School of Medicine  
2007 Joseph E. Johnson Leadership Award American College of Physicians This national award recognizes an Associate member of the College who has demonstrated qualities that exemplify the College’s mission “to enhance the quality and effectiveness of health care by fostering excellence and professionalism in the practice of medicine.”

2009 Elected to Fellow American College of Physicians

**Report of Funded and Unfunded Projects**

**Funding Information**

Past  
2006-2009 Head and Neck Cancer Treatment in the Veterans Affairs (VA): Evaluation of Treatment Patterns, Outcomes, and Costs
Pharmerit  
Co-Investigator  
This pharmacoepidemiology project was designed to describe treatment patterns for patients with locoregionally advanced squamous cell cancer of the head and neck. I oversaw the data collection and analysis and I wrote the paper reporting our findings.

2007-2009 Testosterone Supplementation for Men with Sarcopenia  
NIH, U01AGO14369/CFDA  
Site-PI, $100,000  
This randomized controlled clinical trial was designed to investigate whether testosterone gel could increase muscle strength among men with sarcopenia and low testosterone.

2007-2009 VISN Collaborative for Improving Hypertension Management with ATHENA-HTN  
VA  
Site-PI, $91,000  
This randomized controlled trial was designed to investigate whether a computerized tool would help primary care providers manage patients with hypertension.

2009 The Association between Statins and Melanoma Recurrence  
Carter Foundation  
Co-Investigator, $30,000  
The major goal of this study was to develop a cohort of patients with melanoma. The project investigated the relationship between medications to lower cholesterol and melanoma incidence and progression.

2009 The Study of Heart and Renal Protection  
Merck, MK-0653  
Site-PI, $30,000  
This international randomized controlled clinical trial was designed to investigate whether cholesterol lowering treatments reduced cardiovascular outcomes among patients with renal disease.

Current  
2008-2011 The Relationship between Statins and Prostate Cancer  
DoD, PC073416  
PI, $390,000  
The major goal of this study is to develop skills to be an independent successful researcher. The projects will investigate the relationship between medications to lower cholesterol and prostate cancer incidence and progression.

Report of Local Teaching and Training  
Teaching of Students in Courses
<table>
<thead>
<tr>
<th>Year</th>
<th>Course Title</th>
<th>Institution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Clinical Epidemiology (AC701.0)</td>
<td>Harvard Medical School, Boston, MA</td>
<td>Tutor for a 2-hr session per week for 4 months</td>
</tr>
<tr>
<td></td>
<td>2nd year medical students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004-06</td>
<td>Epidemiology 242</td>
<td>Harvard School of Public Health, Boston, MA</td>
<td>Teaching Assistant for a 90 minute session per week for 4 months</td>
</tr>
<tr>
<td></td>
<td>MPH students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004-07</td>
<td>Preventive Medicine and Nutrition (PM711.0)</td>
<td>Harvard Medical School, Boston, MA</td>
<td>Tutor for a 2-hr session per week for 4 months</td>
</tr>
<tr>
<td></td>
<td>2nd year medical students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009-06</td>
<td>Measuring and Analyzing the Outcomes of Health Care (HPM 530)</td>
<td>Harvard School of Public Health, Boston, MA</td>
<td>Lecturer for a 120 minute session</td>
</tr>
<tr>
<td></td>
<td>MPH students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Introduction to Epidemiology (EP 711 A1)</td>
<td>Boston University School of Public Health, Boston, MA</td>
<td>Lecturer for a 60 minute session</td>
</tr>
<tr>
<td></td>
<td>MPH students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Patient Doctor II (IN761.14)</td>
<td>Harvard Medical School, Boston, MA</td>
<td>Faculty for a 120 minute session</td>
</tr>
<tr>
<td></td>
<td>2nd year medical students</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Clinical Supervisory and Training Responsibilities**

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<tr>
<th>Year</th>
<th>Role and Institution</th>
<th>Hours/Sessionality</th>
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<tbody>
<tr>
<td>2004-05</td>
<td>Primary Care Clinic Preceptor</td>
<td>4 hours per week</td>
</tr>
<tr>
<td>2005</td>
<td>General Medicine Ward Attending</td>
<td>8 hours per day for 2 weeks per year</td>
</tr>
<tr>
<td>2006-07</td>
<td>Adult Diagnostic Treatment Center Preceptor</td>
<td>8 hours per day for 2 months per year</td>
</tr>
</tbody>
</table>

**Formal Teaching of Peers (e.g., CME and other continuing education courses)**

*No presentations below were sponsored by outside entities*

<table>
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<tr>
<th>Year</th>
<th>Title</th>
<th>Institution</th>
<th>Type</th>
</tr>
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<tr>
<td>2008</td>
<td>Screening for Prostate Cancer</td>
<td>Boston University School of Medicine, Boston, MA</td>
<td>Single Presentation</td>
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<tr>
<td></td>
<td>A Core Curriculum in Adult Primary Care Medicine, Boston University</td>
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**Local Invited Presentations**

*No presentations below were sponsored by outside entities*

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<th>Year</th>
<th>Title</th>
<th>Institution</th>
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<tr>
<td>2007</td>
<td>PSA Testing for Prostate Cancer; Grand Rounds</td>
<td>Department of Medicine, VA Boston Healthcare System, Boston, MA</td>
</tr>
<tr>
<td></td>
<td>Department of Medicine, VA Boston Healthcare System, Boston, MA</td>
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</tr>
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</table>

**Report of Regional, National and International Invited Teaching and Presentations**

**Invited Presentations and Courses**

**Regional**


No presentations below were sponsored by outside entities

2007 After a period of intense debate, are physicians ordering PSA tests more frequently? ;
Presenting author (selected abstract)
Boston, MA (Society of General Internal Medicine)

2008 Is High-Density-Lipoprotein Cholesterol Associated with Developing Prostate Cancer?;
Presenting author (selected abstract)
Boston, MA (Society of General Internal Medicine)

2008 Career Panel; Panelist (selected presenter)
Boston, MA (Society of General Internal Medicine)

National

No presentations below were sponsored by outside entities

2003 Resident’s Perspective on Professionalism; Presenter
New Orleans, LA (Accreditation Council for Graduate Medical Education)

2004 Mistakes Residents Notice; Presenter
Chicago, IL (Accreditation Council for Graduate Medical Education)

2004 Student, Resident, and Fellow Career Development Workshop; Presenter
Chicago, IL (Society of General Internal Medicine)

2004 Making things simpler: can non-HDL predict MI as well as LDL-C?; Presenter
St. Louis, IL (Washington University)

2005 Making things simpler: can non-HDL predict MI as well as LDL-C?; Presenter
Pittsburgh, PA (University of Pittsburgh)

2007 The Relationship between Statins and Cancer Incidence in a Veterans Population;
Presenter
Huntington Beach, CA (Southwest Oncology Group, Melanoma Prevention Working Group)

2009 Pharmacoepidemiology in the VA and Beyond; Presenter (Selected Abstract)
Miami, FL (Society of General Internal Medicine)

International

No presentations below were sponsored by outside entities

2010 The principles and pitfalls of working with large administrative databases such as in the
Department of Veterans Affairs; Presenter
Boston, MA (Harvard School of Public Health, Center for Continuing Professional
Education, Measurement, Design, and Analysis Methods for Outcomes Research)

Report of Clinical Activities and Innovations

Current Licensure and Certification

2000 - Medical License

2000 - 2003 Indiana
2003 - Massachusetts

2004 - American Board of Internal Medicine
**Practice Activities**

<table>
<thead>
<tr>
<th>Time</th>
<th>Role</th>
<th>Institution</th>
<th>Hours per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2003 -</td>
<td>Clinician Preventive Cardiology</td>
<td>VA Boston Healthcare System, Boston, MA</td>
<td>4</td>
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<tr>
<td>June 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2006 -</td>
<td>Clinician Primary Care</td>
<td>VA Boston Healthcare System, Boston, MA</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Report of Education of Patients and Service to the Community**

**Activities**

*No activities below were sponsored by outside entities*

2009 American Friends of Kenya / Physician  
I participated in a medical mission with a total of 5 physicians that saw over 900 patients in and around Nairobi, Kenya, over a period of 6 days.

**Report of Scholarship**

**Publications**

**Peer reviewed publications in print or other media**

**Research Investigations**


Non-peer reviewed scientific or medical publications/materials in print or other media

Reviews


Letter to the Editor


Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings


4. Scranton RE, Farwell W, Ezrokhi M, Gaziano JM, Cincotta AH. Quick release bromocriptine (Cycloset™) improves glycaemic control in patients with diabetes failing metformin/sulfonylurea combination therapy. Presented at the European Association for the Study of Diabetes, 2007 international meeting

5. Farwell WR, Sesso HD, Gaziano JM. Is high-density-lipoprotein cholesterol associated with the
risk of developing prostate cancer? Presented at the Society of General Internal Medicine New England Region, 2008 meeting; Presented at the Society of General Internal Medicine, 2008 national meeting

6. Farwell WR, Lawler E, Boulanger L, Cincotta AH, Scranton RE. Assessment of safety for bromocriptine: comparisons of reporting systems and a retrospective cohort study. Presented at the International Society for Pharmacoeconomics and Outcome Research, 2008 international meeting


9. Scranton RE, Farwell WR, Ezrokhi M, Gaziano JM, Cincotta AH. Quick Release Bromocriptine (Cycloset TM) A Novel Treatment for Type 2 Diabetes also Demonstrates Improvements in Blood Pressure. Presented at the International Diabetes Federation, October 2009

10. Paik JM, Farwell WR, Taylor EN. Determinants of plasma parathyroid hormone levels in the National Health and Nutrition Examination Survey. Accepted for presentation at the American Society of Bone and Mineral Research, October 2010

Appendix 2: Analysis plan to explore the relationship between taking lipid modifying treatment and prostate cancer in the Physicians’ Health Study
**Lipid Modifying Treatments and Prostate Cancer**

**Creation of Baseline Population**
PHS II cohort
No pre-randomization cancer, prostate cancer

**Outcome Variable**
(1) Total Cancer
(2) All Forms of Cancer, each listed separately
   - Censor variable (n/y)
   - Time to censor (years)
(3) For Prostate Cancer Specifically,
   - Clinical Stage at Diagnosis
   - Gleason Scores

**Exposure Variables**
(1) Lipid Modifying Treatments
   Enrollment Questionnaire: Self reported treatment: “Are you currently being treated with any cholesterol-lowering medications? (n/y)”
   Statin
   Nonstatin
   Follow-up Questionnaires: “Are you currently taking medications specifically for the following conditions, hypercholesterolemia? (n/y)”

(2) Hypertension
   Enrollment Questionnaire: Self reported treatment: “Are you currently being treated with any medications specifically for hypertension?”
   Follow-up Questionnaire: “Are you currently taking medications specifically for the following conditions, hypertension? (n/y)”

**Baseline Co-Variates (PHS Cohort and PHS II Old Doc Enrollment Questionnaires)**
**Demographics**
Age (years)
Weight (lbs.)
BMI (kg/m²)

**Social**
Smoking (never, former, current; number/day)
Alcohol use (6+/day, 4-5/day, 2-3/day, 1/day, 5-6/week, 2-4/week, 1/week, 1-3/month, rarely/never)
Exercise (daily, 5-6/week, 2-4/week, 1/week, 1-3/month, rarely/never)

**Family Hx**
Prostate cancer (n/y/unknown; age at diagnosis)
Colon or rectal cancer (n/y/unknown; age at diagnosis)
Other cancer (n/y/unknown; age at diagnosis)
MI (n/y/unknown; age at diagnosis)

Co-morbid conditions
Hypertension (self-reported; SBP, DBP)
Hypercholesterolemia (self-reported; total cholesterol, HDL cholesterol)
MI (n/y)
Stroke (n/y)
PTCA (n/y)
Angina (n/y)
CABG (n/y)
Diabetes mellitus (n/y)
TIA (n/y)
Carotid artery surgery (n/y)
Other peripheral artery surgery (n/y)
Abdominal aortic aneurysm (n/y)
Benign prostatic hyperplasia (n/y; mm/yyyy)
Benign prostatic hyperplasia surgery (n/y; mm/yyyy)
Vasectomy (n/y; mm/yyyy)
Prostatitis (n/y; mm/yyyy)
Prostatic infection (n/y; mm/yyyy)

Thanks for your help,

Wildon Farwell
617-232-9500, ext 46182
wildonf@hotmail.com
In 2010, it is estimated that 217,730 men will be diagnosed with prostate cancer and 32,050 men will die of prostate cancer (1). Prostate cancer is the most commonly diagnosed cancer among men, excluding nonmelanoma skin cancer, and is the second most common cause of cancer-related mortality (1). Although prostate cancer is prevalent and a common cause of cancer-related mortality, few prevention strategies for prostate cancer currently exist.

One potential prevention strategy for prostate cancer is taking a statin, 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor. Several recent published studies have reported that statin use may be associated with a decreased risk for advanced prostate cancer (2–5). Platz et al. (2) found a statistically significant inverse relationship between statins and metastatic prostate cancer. Other studies (3–5) have shown that statin use was associated with a decreased Gleason score at prostate cancer diagnosis. However, most recently, one study (6) did not find that statin use was associated with decreased risk for advanced prostate cancer. Unfortunately, a limitation of several of these studies is the potential healthy user bias (7,8). Compared with nonusers, patients who use statins may have a different risk profile for prostate cancer. For example, statin users may have different access to health care, including use of preventive health services such as prostate-specific antigen (PSA) testing (8,9); different competing risks; and different diet and exercise habits compared with nonusers. This bias may result in statin users appearing to have a decreased risk for advanced prostate cancer when in fact something else that is associated with statin use and different from the comparison population may be responsible for the decrease in risk.

A recent study has shown that low serum cholesterol is associated with a decreased risk for advanced prostate cancer compared with high serum cholesterol (10). Platz et al. (10) found a statistically significant direct relationship between higher levels of serum cholesterol and increased risk for high-grade prostate cancer, which supports the hypothesis that taking a medicine to lower cholesterol levels may prevent advanced prostate cancer. However, several questions remain about the relationship between statins,
**CONTEXT AND CAVEATS**

**Prior knowledge**
The association between statin use and the prevention of prostate cancer is unclear.

**Study design**
The electronic and administrative files of a large cohort of men taking a statin or antihypertensive medication were obtained from the Veterans Affairs New England Healthcare System. Prostate cancer incidence among these two patient populations was compared.

**Contribution**
Statin use was associated with a lower risk of total and high-grade prostate cancer. Increased serum cholesterol levels were associated with an increased risk for total and high-grade prostate cancer.

**Implications**
Further studies should be done to investigate the role of cholesterol in high-grade prostate cancer. Statins are a potential preventive therapy for prostate cancer and should be investigated in clinical trials.

**Limitations**
There are few reports of an association between serum cholesterol and prostate cancer incidence; further studies are necessary to confirm these results. It is unknown if and how often patients took their medications.

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From the Editors

cholesterol, and prostate cancer. After attempting to control for a potential healthy user bias, is statin use associated with decreased incidence of high-grade prostate cancer? Is there a dose response between statins and the incidence of high-grade prostate cancer? Are lipid parameters such as high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C associated with the incidence of high-grade prostate cancer or is total cholesterol (TC) alone associated with the incidence of high-grade prostate cancer? Therefore, we built on our previously published analysis of statins and cancer diagnosis to specifically examine the relationship between statins and pathology-confirmed prostate cancer diagnosis and grade. Furthermore, we examined the relationship between several different lipid parameters and pathology-confirmed prostate cancer diagnosis and grade.

**Methods**

**Data Source and Definition of Outcome**
We assembled a retrospective cohort of male patients aged 18 years and older in the Veterans Affairs (VA) New England Healthcare System between January 1, 1997, and December 31, 2007, using national and regional databases. The study protocol was reviewed and approved by the Institutional Review Board of the VA Boston Healthcare System, and the board granted our study a waiver from obtaining informed consent from the patients. We obtained patient level data from the VA National Patient Care Database and the VA Pharmacy Benefits Management System. Patient level data captured in the VA national database system include both inpatient and outpatient demographic characteristics, visits, diagnoses, procedures, medications, and laboratory test results. We defined the cohort entry date as the first recorded prescription fill date for the medication of interest. All patients with a cancer diagnosis were defined by *International Classification of Diseases (ICD)* codes. *ICD-Ninth Revision, Clinical Modification (ICD-9-CM)* codes 140.XX–208.XX or VA pathology-confirmed prostate cancer diagnosis, on or before the cohort entry date, were excluded from the study analyses. An observation period for each patient was defined as beginning 2 years after their entry date and continuing until 1) the first occurrence of a diagnosis of prostate cancer; 2) an ICD-9-CM code for a cancer other than prostate cancer or nonmelanoma skin cancer; 3) 1 year after the last fill date for a medication of interest; 4) death; or 5) the end of the cohort, December 31, 2007. To diminish any potential effects of latent cancer on our predictor variables, we excluded patients that were diagnosed with cancer within 2 years after their potential entry date. Because long-term exposure would likely be required for any medication to reduce prostate cancer incidence, we also excluded all patients who discontinued their medication of interest within 2 years after their potential entry date.

The primary outcomes of our analyses were prostate cancer incidence and Gleason grade. Patients with prostate cancer and the corresponding Gleason grade of their tumors were identified in the electronic medical record of the VA New England Healthcare System using the Automated Retrieval Console (11). Briefly, from a dataset of patients with an ICD-9-CM code for prostate cancer, Automated Retrieval Console identified pathology reports consistent with prostate cancer. Automated Retrieval Console was able to separate reports consistent with a biopsy from reports consistent a prostatectomy. We then used natural language processing to identify Gleason grade within these reports. If we identified a pathology report consistent with prostate cancer, we defined that patient as having been diagnosed with prostate cancer on the date of the pathology report. We further stratified our outcome by high- and low-grade prostate cancer. Low-grade prostate cancer was defined as a total Gleason score of less than or equal to 7 (3 + 4), and high-grade prostate cancer was defined as a total Gleason score of greater than or equal to 7 (4 + 3). Our method of identifying prostate cancer grade was found to have 97% recall and 95% precision (11).

**Predictor Variables**
Patients were selected among active users of the VA New England Healthcare System who 1) filled at least two prescriptions (generally a 90-day supply) for any antihypertensive medication or statin within 1 year, 2) continued filling at least yearly prescriptions for an identified medication of interest, and 3) were seen at least once per year in an outpatient VA clinic. Antihypertensive medication users were defined as patients who never filled a prescription for any cholesterol-lowering medication but filled prescriptions from the following classes of antihypertensive medications: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, alpha blockers, loop diuretics, thiazide diuretics, and centrally active antihypertensive medications. Statin users were defined as patients who filled prescriptions for
any of the following medications: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. Statin users may have been prescribed antihypertensive medication in addition to their cholesterol-lowering medication.

Several potential confounders were documented before or at the start of the observation period. Diabetes mellitus was coded present or absent in the analysis on the basis of the presence or absence of ICD-9-CM code, 250.XX, and a filled prescription for a medication from any of the following classes of medications: insulin, sulfonylurea, biguanide, thiazolidinedione, alpha-glucosidase inhibitor, and meglitinide. Cardiovascular disease was coded present or absent in the analysis on the basis of the presence or absence of ICD-9-CM codes, 410.XX–412.XX, 414.XX, 428.XX–438.XX, or 441.XX–444.2X. We defined aspirin use (yes or no) as an active prescription at the cohort entry date for any of the following agents: aspirin, aspirin buffered oral, aspirin oral enteric coated, and aspirin suppository. We defined finasteride use (yes or no) as an active prescription for finasteride at the cohort entry date. We defined PSA testing (yes or no) as having had a PSA test within 1 year before the cohort entry date and within the 2-year observation period. We defined having had a prostatectomy as the presence or absence of a surgical pathology report consistent with a prostatectomy after a diagnosis of prostate cancer. We extracted information from the electronic medical record on smoking history (yes, no, or unknown), age (years), weight (in kilograms), and height (in meters) at entry into the observation period. We identified measured serum values for TC, LDL-C, and HDL-C within 6 months before each patient’s cohort entry date. We calculated non-HDL-C by subtracting HDL-C from TC among those patients who had both lipid parameters measured on the same day.

**Statistical Analysis**

We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer incidence among statin users compared with the referent group, antihypertensive medication users. A Kaplan–Meier curve was created and reviewed to confirm the assumption of proportionality. Multivariable models for prostate cancer incidence among statin users compared with antihypertensive medication users included age, race, smoking history, prescription for aspirin, prescription for finasteride, PSA testing, diabetes mellitus, and total serum cholesterol. We also calculated a propensity score for being prescribed a statin using a logistic regression model with the same variables as listed above for the multivariable model. The c-statistic for the propensity score model was 0.79. We constructed models to predict prostate cancer incidence that included the propensity score among our entire cohort and the population within the fifth and 95th percentile of propensity score.

To further investigate the relationship between statin dose and prostate cancer incidence, we defined groups of patients by statin use within categories of equivalent simvastatin dosages, the most commonly used statin in our cohort (antihypertensive medication users, ≤10 mg equivalent simvastatin dose, 20 mg equivalent simvastatin dose, and ≥40 mg equivalent simvastatin dose) as previously described (12,13). Briefly, to allow time for a patient to achieve a stable statin dose, categories of equivalent simvastatin dosages were calculated on the basis of the dose and type of statin prescribed at 1 year after treatment initiation. Equivalent simvastatin dosages were calculated by dividing lovastatin and pravastatin doses by 2, dividing the fluvastatin dose by 4, and multiplying the atorvastatin dose by 2. We then determined the hazard ratio and 95% confidence interval of each tertile of equivalent simvastatin dose compared with our referent group for prostate cancer incidence. We controlled for the same potential confounders listed for our models described above. We calculated tests of trend across categories of equivalent simvastatin dose with the median dose in each category acting as an ordinal variable.

We also examined the relationship between serum lipid parameters at baseline and prostate cancer incidence. We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for prostate cancer incidence by continuous measures and quartiles of each lipid parameter. Multivariable models contained all of the previously mentioned variables except that for each lipid parameter, the lipid parameter of interest was exchanged for TC. We calculated tests of trend across quartiles of each lipid parameter with the median value in each quartile acting as an ordinal variable. Quartiles of TC were defined as: <176, 176–206, 207–237, and >237 mg/dL. Quartiles of HDL-C were defined as: <37, 37–42, 43–51, and >51 mg/dL. Quartiles of non-HDL-C were defined as: <131, 131–160, 161–192, and >192 mg/dL. Quartiles of LDL-C were defined as: <105, 105–131, 132–158, and >158 mg/dL. We created similar models to those listed above to examine the relationship between statin use and each lipid parameter with low- and high-grade prostate cancer incidence.

All statistical tests were two-sided and considered statistically significant if \( P \) is less than .05. Statistical tests were performed using SAS, version 9.1 (SAS, Cary, NC).

**Results**

We identified a cohort of 55,875 male patients who met our entry criteria. The mean age was 66.0 years (SD = 11.0 years) and median total follow-up time of 5.6 years (range = 2.0–11.0 years) in the overall cohort (median total follow-up time of 5.2 and 5.6 years was observed among antihypertensive medication users and statin users, respectively). The following is the proportion of each different statin agent in the statin user group 1 year after statin initiation: simvastatin, 54.6%; lovastatin, 43.9%; atorvastatin, 1.2%; pravastatin, 0.2%; and fluvastatin, 0.1%. The mean equivalent simvastatin dose among statin users was 26.2 mg (SD = 22.2 mg). Several characteristics of statin users and users of antihypertensive medications are presented in Table 1.

Among the referent group, 187 (1.3%) of 14,797 patients developed VA pathology-confirmed prostate cancer during their observation period compared with 359 (0.9%) of 41,078 patients taking statins. Overall, Gleason grade was reported in more than 99% of biopsy reports consistent with prostate cancer, and the most common total Gleason grade was 6 (Table 2).

Compared with patients taking antihypertensive medications, the risk of prostate cancer incidence was 31% less among patients taking statins (HR = 0.69, 95% CI = 0.52 to 0.90) after adjusting for age and other potential confounders (Table 3). Statin users
were 14% less likely (HR = 0.86, 95% CI = 0.62 to 1.20) to be diagnosed with low-grade prostate cancer and 60% less likely (HR = 0.40, 95% CI = 0.24 to 0.65) to be diagnosed with high-grade prostate cancer compared with use of antihypertensive medication. The trend for prostate cancer incidence across categories of equivalent simvastatin dose was non-statistically significant (slope = −0.01, \( P_{\text{trend}} = .09 \)), but the risk of prostate cancer incidence was statistically significantly reduced in each category of equivalent simvastatin dose compared with patients taking antihypertensive medications. No apparent dose response among statin users compared with antihypertensive medication users was observed for low-grade prostate cancer incidence (slope = −0.00, \( P_{\text{trend}} = .83 \)). However, for high-grade prostate cancer incidence, the trend across categories was statistically significant (slope = −0.03, \( P_{\text{trend}} = .005 \)) and the risk in each category was statistically significantly reduced. Patients in the highest category of equivalent simvastatin dose were found to have a 73% decreased risk (HR = 0.27, 95% CI = 0.11 to 0.67) for high-grade prostate cancer compared with patients taking antihypertensive medications. Results from the overall cohort and between the fifth and 95th percentile of propensity score adjusted for the propensity score did not differ markedly from the results of our multivariable model (data not shown).

Increased levels of baseline TC appeared to increase the risk of total and high-grade prostate cancer incidence (Table 4). Every 10 mg/dL increase of baseline TC was associated with 2% increased risk of total prostate cancer (HR = 1.02, 95% CI = 1.00 to 1.05) and 6% increased risk of high-grade prostate cancer (HR = 1.06, 95% CI = 1.02 to 1.10). The highest quartile of TC at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.07 to 1.97) and a 204% increased risk of high-grade prostate cancer (HR = 3.04, 95% CI = 1.65 to 5.60). TC was not associated with low-grade prostate cancer. Every 10 mg/dL increase of HDL-C at baseline was associated with 10% increased risk of total prostate cancer (HR = 1.10, 95% CI = 1.02 to 1.19) and 11% increased risk of low-grade prostate cancer (HR = 1.11, 95% CI = 1.02 to 1.21). The highest quartile of HDL-C at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.08 to 1.95) and 157% increased risk of high-grade prostate cancer (HR = 2.57, 95% CI = 1.49 to 4.42). The highest quartile of LDL-C at baseline was associated with a 58% increased risk of total prostate cancer (HR = 1.58, 95% CI = 1.15 to 2.17) and 154% increased risk for high-grade prostate cancer (HR = 2.54, 95% CI = 1.34 to 4.81).

**Discussion**

Among patients in the New England VA Healthcare System, our study found that statin users were at lower risk for total and specifically high-grade prostate cancer incidence compared with users of antihypertensive medications. Furthermore, there was an inverse relationship between the dose of statin achieved at 1 year and the incidence of high-grade prostate cancer. We also found a strong direct relationship between baseline TC and total and high-grade prostate cancer. These findings are all consistent with the hypothesis that cholesterol plays an important role in total and high-grade prostate cancer incidence and medications that lower cholesterol, specifically statins, may reduce the risk of total and high-grade prostate cancer.

Previous observational studies have not clarified the relationship between statins and prostate cancer. Most of these studies only examined the relationship between statins and total prostate cancer and did not specifically investigate the relationship between statins and high-grade prostate cancer. Platz et al. (2) did examine the relationship between advanced prostate cancer patient statin use and metastasis and death and found a statistically significantly decreased risk for advanced prostate cancer among patients taking statins. To date, there are no reports of clinical trials of statins for prostate cancer prevention. One multicenter randomized placebo controlled clinical trial is examining the relationship between statins and prostate cancer biomarkers among men with Gleason

**Table 1. Characteristics of patients taking an antihypertensive medication or statin (N = 55875)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antihypertensive users (n = 14797)</th>
<th>Statin users (n = 41078)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>White</td>
<td>65.2 (12.7)</td>
<td>66.3 (10.4)</td>
</tr>
<tr>
<td>Black</td>
<td>7853 (53.1)</td>
<td>27319 (54.3)</td>
</tr>
<tr>
<td>Other</td>
<td>604 (4.1)</td>
<td>1007 (2.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>51 (0.3)</td>
<td>74 (0.2)</td>
</tr>
<tr>
<td>Smoker, No. (%)</td>
<td>3573 (24.2)</td>
<td>9039 (22.0)</td>
</tr>
<tr>
<td>Aspirin use, No. (%)</td>
<td>4310 (29.1)</td>
<td>15571 (37.9)</td>
</tr>
<tr>
<td>Finasteride use, No. (%)</td>
<td>1424 (9.6)</td>
<td>3733 (9.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>1321 (8.9)</td>
<td>9299 (22.6)</td>
</tr>
<tr>
<td>Cardiovascular disease, No.</td>
<td>4697 (31.7)</td>
<td>24469 (59.6)</td>
</tr>
<tr>
<td>Prostate-specific antigen test, No. (%)</td>
<td>6516 (44.0)</td>
<td>19131 (46.6)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>183.7 (35.4)</td>
<td>213.8 (47.8)</td>
</tr>
<tr>
<td>Non-high-density lipoprotein cholesterol, mg/dL</td>
<td>47.8 (15.1)</td>
<td>44.1 (11.2)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>136.4 (32.8)</td>
<td>168.7 (46.5)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>108.8 (28.8)</td>
<td>136.1 (39.1)</td>
</tr>
</tbody>
</table>

**Table 2. Percentages of Gleason scores (N = 546)**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Antihypertensive users No. (%)</th>
<th>Statin users No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>4</td>
<td>2 (1.1)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>5</td>
<td>4 (2.1)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>6</td>
<td>84 (44.9)</td>
<td>184 (61.3)</td>
</tr>
<tr>
<td>7 (3 + 4)</td>
<td>42 (22.5)</td>
<td>87 (24.2)</td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>22 (11.8)</td>
<td>34 (9.5)</td>
</tr>
<tr>
<td>8</td>
<td>19 (10.2)</td>
<td>32 (8.9)</td>
</tr>
<tr>
<td>9</td>
<td>13 (7.0)</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td>10</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
### Table 3. Prostate cancer outcomes by use of antihypertensives, statins, and categories of equivalent simvastatin doses*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antihypertensive users</th>
<th>Statin users</th>
<th>Categories of equivalent simvastatin doses, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total prostate cancer</td>
<td>187</td>
<td>359</td>
<td>187</td>
</tr>
<tr>
<td>No. of patients</td>
<td>52,403</td>
<td>147,512</td>
<td>52,403</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>1.0 (referent)†</td>
<td>0.69 (0.52 to 0.90)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Low-grade prostate cancer‡</td>
<td>132</td>
<td>284</td>
<td>132</td>
</tr>
<tr>
<td>No. of patients</td>
<td>52,257</td>
<td>147,313</td>
<td>52,257</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>1.0 (referent)</td>
<td>0.86 (0.62 to 1.20)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>High-grade prostate cancer§</td>
<td>55</td>
<td>75</td>
<td>55</td>
</tr>
<tr>
<td>No. of patients</td>
<td>52,403</td>
<td>147,512</td>
<td>52,403</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>1.0 (referent)</td>
<td>0.40 (0.24 to 0.65)</td>
<td>1.0 (referent)</td>
</tr>
</tbody>
</table>

* Models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), history of prostate-specific antigen test (yes or no). CI = confidence interval; HR = hazard ratio.

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥7 (4 + 3).
### Table 4. Prostate cancer outcomes by lipid parameters*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Continuous</th>
<th>Quartiles of lipid parameters</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>10 units</td>
<td>&lt;176 mg/dL</td>
<td>176–206 mg/dL</td>
<td>207–237 mg/dL</td>
<td>&gt;237 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total prostate cancer</td>
<td>No. of patients</td>
<td>349</td>
<td>72</td>
<td>86</td>
<td>81</td>
<td>110</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>112 178</td>
<td>24 985</td>
<td>27 644</td>
<td>28 404</td>
<td>31 145</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (1.00 to 1.05)</td>
<td>1.0 (referent)†</td>
<td>1.13 (0.84 to 1.54)</td>
<td>1.16 (0.85 to 1.58)</td>
<td>1.45 (1.07 to 1.97)</td>
<td></td>
</tr>
<tr>
<td>Low-grade prostate cancer‡</td>
<td>No. of patients</td>
<td>264</td>
<td>55</td>
<td>61</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>111 939</td>
<td>24 937</td>
<td>27 569</td>
<td>28 369</td>
<td>31 064</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.01 (0.98 to 1.04)</td>
<td>1.0 (referent)</td>
<td>0.99 (0.69 to 1.42)</td>
<td>1.10 (0.78 to 1.56)</td>
<td>1.14 (0.80 to 1.63)</td>
<td></td>
</tr>
<tr>
<td>High-grade prostate cancer§</td>
<td>No. of patients</td>
<td>85</td>
<td>17</td>
<td>25</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>112 178</td>
<td>24 984</td>
<td>27 644</td>
<td>28 404</td>
<td>31 145</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.06 (1.02, 1.10)</td>
<td>1.0 (referent)</td>
<td>1.66 (0.93, 2.98)</td>
<td>1.27 (0.62, 2.59)</td>
<td>3.04 (1.65, 5.60)</td>
<td></td>
</tr>
<tr>
<td><strong>HDL-cholesterol</strong></td>
<td>10 units</td>
<td>&lt;37 mg/dL</td>
<td>37–42 mg/dL</td>
<td>43–51 mg/dL</td>
<td>&gt;51 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total prostate cancer</td>
<td>No. of patients</td>
<td>313</td>
<td>69</td>
<td>65</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>97 911</td>
<td>23 641</td>
<td>24 927</td>
<td>23 489</td>
<td>25 853</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.10 (1.02 to 1.19)</td>
<td>1.0 (referent)</td>
<td>1.19 (0.85 to 1.65)</td>
<td>1.51 (1.13 to 2.02)</td>
<td>1.45 (1.08 to 1.95)</td>
<td></td>
</tr>
<tr>
<td>Low-grade prostate cancer</td>
<td>No. of patients</td>
<td>239</td>
<td>55</td>
<td>47</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>97 714</td>
<td>25 815</td>
<td>23 439</td>
<td>24 875</td>
<td>23 586</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.11 (1.02 to 1.21)</td>
<td>1.0 (referent)</td>
<td>0.98 (0.66 to 1.44)</td>
<td>1.48 (1.07 to 2.05)</td>
<td>1.18 (0.83 to 1.68)</td>
<td></td>
</tr>
<tr>
<td>High-grade prostate cancer</td>
<td>No. of patients</td>
<td>74</td>
<td>14</td>
<td>18</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>97 911</td>
<td>25 853</td>
<td>23 489</td>
<td>24 927</td>
<td>23 641</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.10 (0.94 to 1.28)</td>
<td>1.0 (referent)</td>
<td>2.11 (1.13 to 3.95)</td>
<td>1.56 (0.81 to 3.01)</td>
<td>2.57 (1.49 to 4.42)</td>
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</tr>
<tr>
<td><strong>Non-HDL-cholesterol</strong></td>
<td>10 units</td>
<td>&lt;131 mg/dL</td>
<td>131–160 mg/dL</td>
<td>161–192 mg/dL</td>
<td>&gt;192 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total prostate cancer</td>
<td>No. of patients</td>
<td>240</td>
<td>56</td>
<td>50</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>78 250</td>
<td>17 157</td>
<td>18 774</td>
<td>19 646</td>
<td>22 672</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.99 to 1.05)</td>
<td>1.0 (referent)</td>
<td>0.94 (0.66 to 1.34)</td>
<td>1.30 (0.95 to 1.79)</td>
<td>1.13 (0.80 to 1.60)</td>
<td></td>
</tr>
<tr>
<td>Low-grade prostate cancer</td>
<td>No. of patients</td>
<td>183</td>
<td>41</td>
<td>40</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>78 105</td>
<td>17 129</td>
<td>18 734</td>
<td>19 614</td>
<td>22 628</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (0.96 to 1.04)</td>
<td>1.0 (referent)</td>
<td>1.02 (0.69 to 1.52)</td>
<td>1.21 (0.84 to 1.75)</td>
<td>1.00 (0.67 to 1.48)</td>
<td></td>
</tr>
<tr>
<td>High-grade prostate cancer</td>
<td>No. of patients</td>
<td>57</td>
<td>15</td>
<td>10</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>78 250</td>
<td>17 157</td>
<td>18 774.4</td>
<td>19 646</td>
<td>22 672</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.06 (1.02 to 1.09)</td>
<td>1.0 (referent)</td>
<td>0.68 (0.29 to 1.58)</td>
<td>1.63 (0.86 to 3.10)</td>
<td>1.72 (0.86 to 3.46)</td>
<td></td>
</tr>
<tr>
<td><strong>LDL-cholesterol</strong></td>
<td>10 units</td>
<td>&lt;105 mg/dL</td>
<td>106–131 mg/dL</td>
<td>132–158 mg/dL</td>
<td>&gt;158 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total prostate cancer</td>
<td>No. of patients</td>
<td>279</td>
<td>58</td>
<td>64</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>84 068</td>
<td>17 891</td>
<td>20 083</td>
<td>21 775</td>
<td>24 320</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.98 to 1.05)</td>
<td>1.0 (referent)</td>
<td>1.27 (0.92 to 1.76)</td>
<td>1.41 (1.03 to 1.93)</td>
<td>1.58 (1.15 to 2.17)</td>
<td></td>
</tr>
</tbody>
</table>

(Table continues)
Table 4 (Continued).

<table>
<thead>
<tr>
<th>Quartiles of lipid parameters</th>
<th>Outcome</th>
<th>No. of patients</th>
<th>Person-years of follow-up</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-grade prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.53 (0.77 to 3.02)</td>
<td>1.53</td>
<td>63</td>
<td>24,286</td>
<td>1.36 (0.94 to 1.97)</td>
</tr>
<tr>
<td>2.04 (1.28 to 3.24)</td>
<td>1.32</td>
<td>59</td>
<td>22,174</td>
<td>1.37 (0.96 to 1.95)</td>
</tr>
<tr>
<td>2.54 (1.34 to 4.81)</td>
<td>1.20</td>
<td>52</td>
<td>20,043</td>
<td>1.19 (0.78 to 1.83)</td>
</tr>
<tr>
<td>3.05 (2.30 to 3.99)</td>
<td>1.00</td>
<td>41</td>
<td>17,866</td>
<td>1.00 (0.71 to 1.43)</td>
</tr>
<tr>
<td>3.56 (2.82 to 4.58)</td>
<td>1.00</td>
<td>41</td>
<td>17,866</td>
<td>1.00 (0.71 to 1.43)</td>
</tr>
</tbody>
</table>

* Multivariable models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), aspirin use (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), and history of prostate-specific antigen test (yes or no). CI = confidence interval

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤ 7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥ 7 (4 + 3).

In conclusion, men who use statins appear to be at lower risk for prostate cancer and specifically high-grade prostate cancer than men who use antihypertensive medications. Furthermore, men with higher levels of TC appear to be at higher risk of prostate cancer and specifically high-grade prostate cancer than men with lower levels of TC. Clinical trials should investigate whether statins may prevent prostate cancer and specifically high-grade prostate cancer.

References


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**Notes**

The study sponsors had no role in the collection, analysis, and interpretation of the data; the writing of the article; and the decision to submit the article for publication.

**Affiliations of authors:** Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA (WRF, LDA, EVL, JMG); Division of Aging, Department of Medicine (WRF, RES, EVL, JMG), and Cardiovascular Division and Division of Preventive Medicine, Department of Medicine (JMG), Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Department of Epidemiology, Boston University School of Public Health, Boston, MA (EVL).
Appendix 4: Published Paper from the Early Stage Prostate Cancer Cohort Titled, “The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study.”
The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study

Wildon R. Farwell · Christopher Lourenco · Erika Holmberg · Robert B. Hall · Leonard D’Avolio · Elizabeth V. Lawler · J. Michael Gaziano

Abstract

Objective We examined the relationship between height and prostate cancer grade.

Methods The Early Stage Prostate Cancer Cohort Study is an observational cohort of 1,037 men diagnosed with early-stage prostate cancer, T\textsubscript{0–3}N\textsubscript{x}M\textsubscript{0}. High-grade prostate cancer was defined as a biopsy Gleason score \(\geq 7 (4 + 3)\). Logistic regression models were created to calculate odds ratios (OR) and 95% confidence intervals (CI) for the cross-sectional relationship between height and prostate cancer grade in the overall cohort and subpopulations.

Results We identified 939 participants with a biopsy Gleason score. High-grade prostate cancer was diagnosed in 138 participants. Overall, participants in the highest quartile of height were more than twice as likely to have a Gleason score \(\geq 7 (4 + 3)\) than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), after multivariate adjustment. Participants in the highest quartile of height were more likely to be diagnosed with high-grade prostate cancer than participants in the lowest quartile of height among participants who were black, OR 8.00 (95% CI 1.99, 32.18), and participants who had diabetes mellitus, OR 5.09 (95% CI 1.30, 19.98).

Conclusions Height is associated with increased risk of high-grade prostate cancer overall and perhaps among certain subpopulations.

Keywords Prostatic neoplasms · Body height · Epidemiology

Introduction

Prostate cancer is a significant cause of morbidity and mortality among men. In 2010, it is estimated that 217,730 men were diagnosed with prostate cancer and 32,050 men died as a result of prostate cancer in the United States [1]. Given the large difference between the number of men who are diagnosed with prostate cancer and die from prostate cancer, it would be helpful to identify risk factors for prostate cancer that are more likely to lead to prostate cancer–related mortality. The pathologic grade of prostate cancer at diagnosis is related to the likelihood of prostate cancer mortality [2, 3].

Height is a potential risk factor for prostate cancer. A meta-analysis of 58 studies found that height was positively...
associated with prostate cancer [4]. However, fewer studies have examined the relationship between height and advanced prostate cancer. Among the studies that have examined this relationship, taller men appear to be at higher risk for more advanced prostate cancer than shorter men [4–6] but not all studies have found this association [7, 8], and little is known about this relationship in subpopulations of men with different risks of prostate cancer. Therefore, we examined the relationship between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort. Furthermore, we explored the relationship between height and prostate cancer grade in various subpopulations of men with potentially different risk of high-grade prostate cancer.

Materials and methods

Data sources

Men were eligible for participation in the Early Stage Prostate Cancer Cohort (ESPCC) study if they were diagnosed with early-stage prostate cancer, T0–3N0M0, within two and a half years prior to enrollment. In addition, eligible men had no other history of cancer, with the exception of non-melanoma skin cancer, within 5 years of enrollment and had no other major illness that would have precluded long-term participation. Men with early-stage prostate cancer were identified at 16 sites throughout the VA Healthcare System.

A total of 1,037 men participated in the ESPCC study. Participants completed questionnaires at the initial interview that asked about demographic information including age, race, current weight, and current height; medical history including diabetes mellitus; and other potential risk factors for prostate cancer progression including smoking history and family history of prostate cancer. Questions were also asked about why prostate cancer had been suspected prior to a diagnosis.

Definition of outcome

The Gleason score was identified from pathology reports at the time of diagnosis and prostatectomies that had occurred by the time of the baseline survey. We identified Gleason scores from paper reports sent to us by site coordinators and using the Automated Retrieval Console [9] to review electronic reports in the VA Healthcare System electronic medical record. The appropriate Gleason score for each participant was selected according to the criteria of the 2005 International Society of Urological Pathology Consensus Conference on Gleason grading of prostatic carcinoma [10]. High-grade prostate cancer was defined as a Gleason score ≥ 8 as well as cases where the overall Gleason score was 7 and the primary score was ≥4.

Statistical analyses

We calculated the percent of men in our cohort with and without high-grade prostate cancer as well as the mean age, weight, and height ± standard deviation. We calculated the percent of men with a self-reported age at the time of prostate cancer diagnosis that matched ± 1 year their age identified in the electronic medical record, Veterans Affairs (VA) Patient Treatment File (PTF). We also calculated the percent of men who reported having diabetes mellitus and were found to have diabetes mellitus in the VA PTF at the time of prostate cancer diagnosis. We used logistic regression to examine the relationship between height as a continuous (5 cm) marker and grade of prostate cancer. Quartiles of height were defined, <172.7, 172.7–177.7, 177.8–182.7, and >182.7 cm. We used logistic regression to examine the relationship between quartiles of height and grade of prostate cancer with the lowest quartile as the referent quartile. We calculated the median height in each quartile and used logistic regression to calculate the p for trend across quartiles of height for prostate cancer grade. We performed age- and multivariate-adjusted models to calculate odds ratios (OR) and 95% confidence intervals (CI). Multivariate models controlled for age (years), race (white, black, other), family history of prostate cancer (yes, no, missing), whether the prostate cancer was suspected by PSA testing (yes, no), smoking status (no, current, quit), diabetes mellitus (yes, no), weight (kg), and site of enrollment (sites). We repeated the above procedures among groups stratified by the presence or absence of particular risk factors for high-grade prostate cancer. We dichotomized age and weight based upon the median values in the cohort. We limited the analysis to categories with ≥100 men and calculated the p value for the interaction term of each stratification. We also performed a sensitivity analysis among men who received a prostatectomy using height as a continuous (5 cm) marker and grade of prostate cancer at prostatectomy.

Results

Of the 1,037 participants in the ESPCC, we identified 939 with Gleason scores from biopsy pathology reports and 931 with Gleason scores and reported height. We found that the age at prostate cancer diagnosis that a participant reported and was identified in the VA PTF matched ± 1 year in 95% of the participants. We also found that a diagnosis of diabetes mellitus matched between participant’s self-report and the VA PTF in 88% of participants. Overall, the mean ± standard deviation Gleason score from biopsy reports was 6.3 ± 1.1 units. The mean ± standard deviation height was 177.2 ± 7.1 cm. Taller participants were younger and heavier than shorter participants (Table 1). Taller participants
were more likely to be black and report a history of diabetes mellitus than shorter participants.

We identified 138 participants with a Gleason score ≥7 (4 + 3) at biopsy. Participants in the highest quartile of height were more than twice as likely to have a Gleason score ≥7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), and the trend across quartiles was significant, \( p_{\text{trend}} = 0.01, \) after multivariate adjustment (Table 2). Although not statistically significant, every 5-cm increase was associated with an increased risk for a Gleason score of ≥7 (4 + 3) at biopsy, OR 1.11 (95% CI 0.96, 1.29). Among the 239 men who underwent prostatectomy, every 5-cm increase was also associated with an increased risk for a Gleason score of ≥7 (4 + 3) at prostatectomy, OR 1.07 (95% CI 0.77, 1.48), although not statistically significant.

We examined the relationship between height and prostate cancer grade in various subpopulations (Table 3). Participants younger than age 65 years had a non-significant increased risk for a Gleason score ≥7 (4 + 3) with every 5 cm of height, OR 1.16 (0.90, 1.50), and the participants in the highest quartile of height were more likely, although not statistically significant, to have a Gleason score ≥7 (4 + 3) than participants in the lowest quartile of height, OR 4.06 (0.86, 19.15). Among black participants, every 5 cm of height was associated with an increased risk for a Gleason score of ≥7 (4 + 3) at biopsy, OR 1.44 (1.06, 1.95). Participants in the highest quartile of height were eight times more likely to have a Gleason score ≥7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 8.00 (1.99, 32.18), and the trend across quartiles was significant, \( p_{\text{trend}} < 0.01. \) Among participants with diabetes mellitus, every 5 cm of height was associated with an increased risk for a Gleason score of ≥7 (4 + 3) at biopsy, OR 1.35 (1.00, 1.81). Participants in the highest quartile of height were over five times more likely to have a Gleason score ≥7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 5.09 (1.30, 19.98), and the trend across quartiles was significant, \( p_{\text{trend}} = 0.01. \) Among participants who weighed < 87 kg, participants in the highest quartile of height were over three times more likely to have a Gleason score ≥7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 3.23 (1.24, 8.40), and the trend

<table>
<thead>
<tr>
<th>Table 1 Participant characteristics by quartiles of height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
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<tr>
<td>Age, years, mean ± SD</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD</td>
</tr>
<tr>
<td>Height, cm, mean ± SD</td>
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<tr>
<td>Race, %</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Family history of prostate cancer, %</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>Suspected cancer due to PSA, %</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Smoke, %</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Quit</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Received usual care in the VA Healthcare System, %</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>
IGF-1 levels may differ by age, race, and the presence or absence of diabetes mellitus. It is generally believed that levels of IGF-1 decline with increasing age [20]. McGreevy et al. reported that although plasma levels of IGF-1 were not different between black and white men, the level of IGF-binding protein-3 (IGFBP-3) and the ratio of IGF-1/IGFBP-3 were lower among black men [21]. This suggests that black men may have higher levels of bioavailable IGF-1. Although not all studies have found black men to have a lower ratio of IGF-1/IGFBP-3, several studies have found that black men have lower levels of IGFBP-3 [22–25]. Several cross-sectional studies have found elevated IGF-1 levels and decreased IGFBP-3 levels in patients with impaired glucose tolerance and diabetes mellitus [26, 27]; however, another study found decreased levels of IGF-1 among diabetic men compared with non-diabetic men [28].

One should consider several limitations of our analysis when interpreting our results. Our analysis is cross-sectional. Therefore, based upon our results, we cannot formally say that height is a risk factor for high-grade prostate cancer. However, it is difficult to imagine that high-grade prostate cancer affected a participant’s height in this cohort of men with early-stage prostate cancer. Height was self-reported. However, the correlation between measured and self-reported height is typically high although shorter men tend to overreport their height more frequently than taller men [29]. This over reporting would tend to attenuate the effect of height on prostate cancer grade toward the null hypothesis. Furthermore, we had high correlation between self-reported age and diabetes mellitus and the values for these variables identified in the electronic medical record. This suggests that the height that participants reported was likely accurate. We had small numbers of men with high-grade prostate cancer and focused our analysis on Gleason scores obtained from biopsies rather than prostatectomy. However, we found consistent results whether we used Gleason scores obtained from biopsy or prostatectomy. We were unable to collect pathology reports from biopsies that occurred outside of the VA Healthcare System. Therefore, our analysis is limited to men with early-stage prostate cancer. Height was self-reported. However, it is difficult to imagine that high-grade prostate cancer affected a participant’s height in this cohort of men with early-stage prostate cancer. Height was self-reported. However, the correlation between measured and self-reported height is typically high although shorter men tend to overreport their height more frequently than taller men [29]. This over reporting would tend to attenuate the effect of height on prostate cancer grade toward the null hypothesis. Furthermore, we had high correlation between self-reported age and diabetes mellitus and the values for these variables identified in the electronic medical record. This suggests that the height that participants reported was likely accurate. We had small numbers of men with high-grade prostate cancer and focused our analysis on Gleason scores obtained from biopsies rather than prostatectomy. However, we found consistent results whether we used Gleason scores obtained from biopsy or prostatectomy. We were unable to collect pathology reports from biopsies that occurred outside of the VA Healthcare System. However, we did not find a significant difference in the frequency of participants who reported that they received a majority of their care in the VA Healthcare System by quartiles of height. Our cohort was limited to men with early-stage prostate cancer. Therefore, our results are likely biased toward the null hypothesis and thus underestimate the true effect, since many cases of high-grade prostate cancer likely did not qualify for inclusion in the ESPCC. Although we found several apparent differences in the relationship between height and prostate cancer among various strata of risk factor groups for prostate cancer progression, none of the p values for interaction were significant. However, the interaction coefficient does not discern the balance of potential synergistic, antagonistic, or competitive relationships between variables and thus cannot rule out the presence of an interaction [30].
Table 3  Odds ratios (95% confidence interval) of Gleason score $\geq 7 \ (4 + 3)$ compared with Gleason score $\leq 7 \ (3 + 4)$ at diagnostic biopsy by continuous height and quartiles of height stratified by age, race, and presence or absence of diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Continuous, 5 cm</th>
<th>Quartiles</th>
<th>$p$, Trend</th>
<th>$p$, Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>$&lt;172.7 \text{ cm}$</td>
<td>$172.7–177.7 \text{ cm}$</td>
<td>$177.8–182.7 \text{ cm}$</td>
</tr>
<tr>
<td>Age $&lt;$65 years, $n = 429$</td>
<td>47</td>
<td>4</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>2.07 (0.61, 7.00)</td>
<td>2.56 (0.81, 8.08)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.21 (0.98, 1.49)</td>
<td>Referent</td>
<td>2.07 (0.61, 7.00)</td>
<td>2.56 (0.81, 8.08)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.16 (0.90, 1.50)</td>
<td>Referent</td>
<td>2.07 (0.61, 7.00)</td>
<td>2.56 (0.81, 8.08)</td>
</tr>
<tr>
<td>$\geq$65 years, $n = 498$</td>
<td>90</td>
<td>17</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>0.96 (0.48, 1.94)</td>
<td>1.29 (0.66, 2.53)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.12 (0.96, 1.32)</td>
<td>Referent</td>
<td>0.96 (0.48, 1.94)</td>
<td>1.29 (0.66, 2.53)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.10 (0.92, 1.32)</td>
<td>Referent</td>
<td>0.96 (0.48, 1.94)</td>
<td>1.29 (0.66, 2.53)</td>
</tr>
<tr>
<td>Weight $&lt;$87 kg, $n = 455$</td>
<td>58</td>
<td>13</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>1.11 (0.51, 2.45)</td>
<td>1.47 (0.66, 3.25)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.15 (0.94, 1.41)</td>
<td>Referent</td>
<td>1.11 (0.51, 2.45)</td>
<td>1.47 (0.66, 3.25)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.21 (0.96, 1.52)</td>
<td>Referent</td>
<td>1.11 (0.51, 2.45)</td>
<td>1.47 (0.66, 3.25)</td>
</tr>
<tr>
<td>$\geq$87 kg, $n = 471$</td>
<td>79</td>
<td>7</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>No. of cases, $n = 471$</td>
<td></td>
<td>Referent</td>
<td>1.39 (0.53, 3.70)</td>
<td>1.62 (0.66, 3.99)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.11 (0.93, 1.33)</td>
<td>Referent</td>
<td>1.39 (0.53, 3.70)</td>
<td>1.62 (0.66, 3.99)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.08 (0.88, 1.31)</td>
<td>Referent</td>
<td>1.39 (0.53, 3.70)</td>
<td>1.62 (0.66, 3.99)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>Referent</td>
<td>1.02 (0.33, 3.08)</td>
<td>1.49 (0.55, 4.07)</td>
</tr>
<tr>
<td>White, $n = 727$</td>
<td>96</td>
<td>14</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>1.31 (0.65, 3.80)</td>
<td>1.72 (0.88, 3.37)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.08 (0.92, 1.26)</td>
<td>Referent</td>
<td>1.31 (0.65, 3.80)</td>
<td>1.72 (0.88, 3.37)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.03 (0.86, 1.23)</td>
<td>Referent</td>
<td>1.31 (0.65, 3.80)</td>
<td>1.72 (0.88, 3.37)</td>
</tr>
<tr>
<td>Black, $n = 191$</td>
<td>40</td>
<td>6</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>1.40 (0.31, 6.23)</td>
<td>1.56 (0.37, 6.61)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.37 (1.07, 1.75)</td>
<td>Referent</td>
<td>1.40 (0.31, 6.23)</td>
<td>1.56 (0.37, 6.61)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.44 (1.06, 1.95)</td>
<td>Referent</td>
<td>1.40 (0.31, 6.23)</td>
<td>1.56 (0.37, 6.61)</td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td>0.56</td>
<td>No, $n = 676$</td>
<td>104</td>
<td>15</td>
</tr>
<tr>
<td>No. of cases</td>
<td></td>
<td>Referent</td>
<td>1.21 (0.60, 2.44)</td>
<td>1.88 (0.96, 3.66)</td>
</tr>
<tr>
<td>Age-adj</td>
<td>1.21 (1.03, 1.42)</td>
<td>Referent</td>
<td>1.21 (0.60, 2.44)</td>
<td>1.88 (0.96, 3.66)</td>
</tr>
<tr>
<td>MV*-adj</td>
<td>1.14 (0.94, 1.37)</td>
<td>Referent</td>
<td>1.24 (0.57, 2.69)</td>
<td>1.73 (0.81, 3.70)</td>
</tr>
</tbody>
</table>
Table 3 continued

<table>
<thead>
<tr>
<th>Continuous, 5 cm</th>
<th>Quartiles</th>
<th>p, Trend</th>
<th>p, Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;172.7 cm</td>
<td>172.7–177.7 cm</td>
<td>177.8–182.7 cm</td>
</tr>
</tbody>
</table>

Yes, n = 198

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Age-adj</th>
<th>MV*-adj</th>
<th>Referent</th>
<th>p, Trend</th>
<th>p, Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected cancer due to PSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n = 804</td>
<td>174</td>
<td>1.08 (0.83, 1.39)</td>
<td>0.86 (0.23, 3.22)</td>
<td>0.67 (0.18, 2.49)</td>
<td>1.71 (0.54, 5.39)</td>
<td>0.19</td>
</tr>
<tr>
<td>No, n = 117</td>
<td>17</td>
<td>1.16 (0.80, 1.70)</td>
<td>1.57 (0.34, 7.16)</td>
<td>0.88 (0.16, 4.86)</td>
<td>1.79 (0.37, 8.57)</td>
<td>0.75</td>
</tr>
<tr>
<td>Current or previous, n = 690</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n = 193</td>
<td>38</td>
<td>1.35 (1.05, 1.75)</td>
<td>1.34 (0.36, 4.93)</td>
<td>1.13 (0.35, 3.71)</td>
<td>4.61 (1.48, 14.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No, n = 724</td>
<td>98</td>
<td>1.07 (0.92, 1.25)</td>
<td>1.00 (0.51, 1.94)</td>
<td>1.53 (0.82, 2.87)</td>
<td>1.45 (0.77, 2.74)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Multivariate models included each of the following covariates except for the categorical variable by which the population was stratified: age (years); race (white, black, other); family history of prostate cancer (yes, no, missing); prostate cancer suspected by PSA (yes, no); smoke (no, current, quit); diabetes mellitus (yes, no); weight (kg); site of enrollment (sites)
Conclusions

In the ESPCC, height appeared to be associated with increased risk of high-grade prostate cancer, especially among younger participants, black participants, and participants with diabetes mellitus. Future research should focus on the relationship between height and prostate cancer mortality as well as the potential mechanism for the specific relationship between height and prostate cancer grade among younger men, black men, and men with diabetes mellitus.

Acknowledgments  Supported by research award W81XWH-08-2-0168 from the Department of Defense and grants 601 and 96 from the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development.

References

Appendix 5: IRB Approval
### PROJECT/PROGRAM TITLE:
2P. Request for Continued Approval of Human Studies IRB #2140 “The Relationship between Statins and Prostate Cancer Prevention”

### PRINCIPAL INVESTIGATOR:
Wildon Farwell, M.D.

### VAMC:
VA Boston Healthcare System

### REVIEW DATE:
February 28, 2011

### COMMITTEE FINDINGS:

1. The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or a surrogate who possesses standard reading and comprehension skills.

2. The informed consent is obtained by the principal investigator or a trained and supervised designate under suitable circumstances.

3. Every effort has been made to decrease risk to subject(s)?

4. The potential research benefits justify the risk to subject(s)?

5. If subject is incompetent and surrogate consent is obtained, have all of the following conditions been met; a) the research can’t be done on competent subjects; b) there is no risk to the subject, or if risk exists the direct benefit to subject is substantially greater; c) if an incompetent subject resists, he will not have to participate; d) if there exists any question about the subject’s competency, the basis for decision on competency has been fully described.

6. If the subject is paid the payment is reasonable and commensurate with the subject's contribution.

7. Members of minorities and women have been included in the study population whenever possible and scientifically desirable.

8. Comments: (Indicate if Expedited Review)
This study continues to meet the criteria for waiver of the requirement of informed consent. This study continues to meet the criteria for waiver of HIPAA authorization.

### RECOMMENDATION:
• APPROVE  □ DISAPPROVE / REVISE

### SIGNATURE OF CHAIRMAN
Carole Palumbo, Ph.D. Chair, Human Studies Subcommittee

### DATE:
February 28, 2011
| Date of Action: | February 28, 2011 |
| Principal Investigator: | Wildon Farwell, M.D. |
| Title of Submission: | "The Relationship between Statins and Prostate Cancer Prevention" |
| Protocol Number: | IRB #2140 |
| Type of Submission & Item Description: | Request for Continued Approval of Human Studies. |
| Human Subject Enrollment: | Yes: X  No: |
| Vulnerable Population: | Yes:  No: X  Category: Entire Study: Sub-Population: |
| Sponsor: | DoD |
| Administrator of Funding: | BVARI |

**APPROVED** at IRB meeting

**APPROVED under procedures for expedited review by**

**CHANGES REQUIRED:** Based on Committee review, the changes or actions noted below are stipulated as required for approval. Compliance with these stipulations may be confirmed under Committee procedures for expedited review.

**DEFERRED:** The item has been deferred pending changes or clarifications noted below. The proposal will be reconsidered at the next Committee meeting after the requested information or changes are submitted.

**DISAPPROVED:** The proposal was disapproved for the reasons noted below. Please consult with the ACOS for Research or the Committee Chairperson before resubmitting.

**NOTED**

Note: For 'Changes Required' and 'deferred', responses must be received from the principal investigator within 60 days. After 60 days a new submission and full review are required.

**COMMENTS (2P):**

1. The IRB determined that no conflict of interest for the PI or any other study personnel that may influence the conduct of the research existed previously for this protocol or arose since the last continuing review.
2. This study continues to meet the criteria for waiver of the requirement for informed consent under 38 CFR 16.116(d)
3. This study continues to meet the criteria for waiver of HIPAA authorization under 45 CFR 164.512(i)(2)
4. This study has been designated as minimal risk and one year approval.
6. The IRB determined that future 'Requests for Continuing Review' qualify for approval under expedited review procedures.
7. Additional requirements for Department of Defense studies have been met.

Carole Palumbo, Ph.D.
Chair, Human Studies Subcommittee