Statin Drug Use is Not Associated with Prostate Cancer Risk in Men Who are Regularly Screened

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Purpose: Prospective cohort studies support the hypothesis that statin drug users have a lower risk of aggressive prostate cancer. Whether statin drug use influences the risk of screen detected disease is less clear, possibly because of complex detection biases. Thus, we investigated this association in a setting in which men had low baseline serum prostate specific antigen concentration and were screened annually.

Materials and Methods: We performed a cohort study of 9,457 men 55 years old or older at randomization to the placebo arm of PCPT (Prostate Cancer Prevention Trial). The men reported new use of medications quarterly. We estimated the multivariable adjusted HR of prostate cancer (574 cases in 62,192 person-years) for statin drug use and duration of use during the trial using Cox proportional hazards regression.

Results: During 7 years of followup statin drug use during the trial was not associated with the risk of total prostate cancer (HR 1.03, 95% CI 0.82–1.30), or lower grade (HR 0.96, 95% CI 0.71–1.29) or higher grade (HR 1.27, 95% CI 0.85–1.90) prostate cancer. Duration of use during followup was also not associated with the risk of total, or lower or higher grade disease (p trend = 0.7, 0.5 and 0.2, respectively).

Conclusions: These prospective results do not support the hypothesis that statin drugs protect against prostate cancer in the setting of regular prostate cancer screening.

Key Words: prostate, hydroxymethylglutaryl-coA reductase inhibitors, prostatic neoplasms, risk, mass screening

Abbreviations and Acronyms

BMI = body mass index

NSAID = nonsteroidal anti-inflammatory drug

PCPT = Prostate Cancer Prevention Trial

PSA = prostate specific antigen

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Study received institutional review board approval at PCPT participating centers and the Johns Hopkins Bloomberg School of Public Health.

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SEVERAL prospective cohort studies support the hypothesis that men who use cholesterol lowering statin drugs (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), especially for a longer duration, have a lower risk of prostate cancer with a more aggressive phenotype[1–3] or prostate cancer diagnosed at more advanced stage in the absence of screening.[4] In contrast, the

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association between statin use and prostate cancer overall, especially early stage disease, is not consistent.[1] The lack of consistency may have arisen from differences in the extent to which a complex set of detection biases operate. Detection bias in these studies could have resulted from the possible influence of statins on serum PSA[5,6] and from the tendency of men seeking medical care to receive regular screening for elevated cholesterol and PSA.[7]

To evaluate whether statins influence prostate cancer risk in the setting of regular screening for the disease and in which detection bias is less likely to be operating, we performed a prospective cohort study in the PCPT placebo arm. Unlike standard cohorts the PCPT protocol called for annual PSA screening and prostate digital rectal examination during the 7 years of the trial.[8] Thus, the opportunity to detect prostate cancer was less influenced by factors (eg medical care uptake) that may be correlated with statin use than in other studies.

METHODS

Study Design and Population

We included in this prospective cohort study all 9,457 men randomized to the placebo arm of the multicenter, SWOG coordinated PCPT.[8] PCPT tested whether the 5α-reductase type II inhibitor finasteride would prevent prostate cancer in 18,882 men 55 years old or older with normal digital rectal examination and serum PSA 3.0 ng/ml or less. To be eligible for analysis men could not have been diagnosed with cancer except for nonmelanoma skin cancer. Institutional review boards at participating centers approved PCPT. Approval for this secondary analysis was received from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Assessment of Statin Use, PSA and Other Factors

The men were asked to complete a survey about demographic characteristics, lifestyle and medical history during the entry visit. At most study centers the men were asked to complete a food frequency questionnaire during the next annual visit. At the entry visit height and weight were measured using standardized protocols. Weight was measured at each annual visit. Waist and hip circumferences were measured at the first annual visit after the entry visit.

At study entry current medication use was assessed by interview using closed (eg aspirin and hypertension drugs) and open-ended questions. At each 6-month and annual clinic visit, and each 3 and 9-month telephone calls between clinic visits the men were asked, "Have you started any new medications since we last talked with you?" We coded as a statin any of certain brand or generic medication names, including Lescol® (fluvastatin), Lipitor® (altorvastatin), Altoprev®, Mevacor®, Advicor® (each lovastatin), Pravachol® (pravastatin), Zocor® (simvastatin), Baycol (cerivastatin, Bayer, Leverkusen, Germany) or statin. Other cholesterol lowering drugs, ie Gemcor, Lopid (each gemfibrozil), Tricor® (fenofibrate), Colestid® (colestipol) and nonspecific drugs (ie cholesterol drug, cholesterol lowering drug and high cholesterol drug) were not included. Because the interviews requested new medication use, to determine statin use and calculate duration of use during the trial, we assumed that after a man reported receiving a statin he continued receiving it until the end of the trial. We also assumed that the date that a man reported first use of a drug was the date that he began receiving it. We had no information on use before baseline in 1993 to 1997. The earliest possible statin use was 1987, the year that it was first available on the market.[9,10]

As a component of the trial protocol, serum PSA was measured at a central laboratory (Esoterix, Calabasas Hills, California) in samples collected at the entry visit and annually thereafter. Serum total cholesterol was measured in the sample collected at the entry visit.[11]

Ascertainment of Prostate Cancer Cases

We included as cases those detected on prostate biopsy performed for a clinical indication, usually increased PSA and/or abnormal digital rectal examination. We did not include as cases those detected on the end of study biopsy performed without clinical indication per PCPT protocol[8] since these cases otherwise would not have been detected during the trial. Biopsies were reviewed by pathologists at the study center and confirmed at the Prostate Diagnostic Laboratory, University of Colorado. We used the Gleason score determined by central review.

Statistical Analysis

We calculated the age adjusted mean and prevalence of baseline characteristics by statin use during the trial using linear regression. We estimated the percent difference in serum PSA (repeated measures) between use and never use of a statin during the trial (updated but truncated at the date of prostate cancer diagnosis) using generalized estimating equations with an autoregressive correlation structure.

We estimated the HR and 95% CI of total, localized (T1 or T2, and N0 and M0 in 507 men), Gleason 2-6 (lower grade in 351) and Gleason 7-10 (higher grade in 156) prostate cancer detected on biopsy performed for clinical indication using Cox proportional hazards regression. Few men were diagnosed with advanced stage disease, including 5 with T3N0M0, 3 with N^+M0 and 6 with M^+, because the trial eligibility criteria and screening protocol precluded such analysis. We evaluated statin use during the trial (use vs never) and duration of statin use during the trial (never, 0 to less than 4 years and 4 years or greater) as time dependent variables. Time at risk began to accrue at the trial entry date and ended on the date of diagnosis or censor, whichever was first. Men diagnosed with prostate cancer on an end of study biopsy performed without clinical indication per trial protocol[8] were censored at the date of diagnosis. Men not diagnosed with prostate cancer were censored at the end of study date (7 years) or the date of last trial contact.

We report age and multivariable adjusted results. The final multivariable models included factors selected a priori based on likely associations with prostate cancer and/or statin use, including age in years (continuous),