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Minimal detection bias in the inverse association between statin drug use and advanced prostate cancer risk: A simulation study

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Abstract

Background—Prospective studies support that statins may protect against advanced prostate cancer. Detection bias arising from higher PSA screening rates among statin users vs. non-users could produce an inverse association for advanced disease. Thus, we conducted simulations to assess whether this source of bias is explanatory.

Methods—3,000 datasets with 100,000 men without prostate cancer were simulated for populations with high (65%) or low (15%) PSA screening. We investigated three scenarios: $RR_{true} = 1.0, 0.75,$ and 0.5 for statins and advanced disease (1.0 for localized). We set the statin prevalence to 10% and varied the percentage of users who were PSA screened (0 – 100%). We assumed an annual total prostate cancer incidence of 1%, with risk in screened men twice that of unscreened men, and an advanced stage at diagnosis in 20% and 40% of cases in screened and unscreened men, respectively.

Results—As PSA screening and statin use became more coincident, the $RR_{observed}$ for local and total prostate cancer was biased upward from the RR_{true} of 1.0, especially when the prevalence of PSA screening was low. However, in all simulated scenarios, there was little downward bias for advanced disease (e.g., if $RR_{true} = 1.0$ and 70% of statin users and either 65% or 15% of the population overall was PSA screened, then $RR_{observed} = 0.98$ for both).

Conclusions—Given our assumptions, this simulation suggests that this source of detection bias is unlikely to explain the reported inverse association between statins and advanced prostate cancer, but may explain the positive association for total prostate cancer that has been reported in some studies.

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Conflict of Interest Statement

We have no conflicts of interest to disclose.

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Keywords

Hydroxymethylglutaryl-CoA Reductase Inhibitors; Prostatic Neoplasms; prostate-specific antigen

Introduction

Recent prospective studies support the hypothesis that statin drugs (HMG Co-A reductase inhibitors) may protect against the development of advanced prostate cancer [1–6], although a few studies disagree. [7,8] The findings for statin drug use and overall prostate cancer have been less consistent [1–17]. Further, some studies suggest that statins may also protect against high-grade prostate cancer. [1,13]

However, one important concern is that the inverse findings for advanced disease may be due, wholly or in part, to detection bias. In countries like the US, men are likely to receive screening for both elevated PSA and cholesterol from their internists and, therefore, are likely to both be prescribed a statin and undergo diagnostic workup for prostate cancer. Thus, men taking a statin may be less likely to be diagnosed with advanced prostate cancer, irrespective of a causal relationship (Figure 1).

Ideally, this bias would be precluded by studying this association in the pre-PSA era. However, this is not possible in the US because statin drugs and PSA screening, that is, testing for elevated PSA in asymptomatic men, became available to the public at approximately the same calendar time (late 1980s). [18] Men do not routinely undergo PSA screening in other countries, although it is available, so the extent of detection bias may differ. Nevertheless, a study in the Finnish population, which has a comparatively low (15%) prevalence of PSA screening, found a comparable inverse association between statin use and advanced prostate cancer that US studies have reported. [4] However, it is unclear whether PSA-associated detection bias may still explain these results even in this setting of a low prevalence of PSA screening.

Thus, we performed a simulation study to determine whether detection bias might explain, wholly or in part, the observed inverse association between statin drug use and advanced prostate cancer in observational studies.

Methods

Assumptions

We simulated 3,000 closed cohort datasets (Figure 2) with 100,000 older men without a prostate cancer diagnosis for two populations, one with a high (65%) and one with a low (15%) prevalence of routine screening for elevated PSA, as in the US [1] and Europe, [4] respectively. For the purposes of this simulation, we assumed that men were either undergoing annual screening or were not screened at all. For both populations we investigated three scenarios for the true association between statin drug use and advanced prostate cancer: 1) a relative risk of 1.0, 2) a relative risk of 0.75, and 3) a relative risk of 0.5; we chose these numbers because when we calculated the summary point estimate for all the studies of advanced prostate cancer using inverse variance weighting we found that it was approximately 0.75 [1–8], and the point estimate for the association in the study by Platz et al. is approximately 0.5 [1]. In each scenario, we set the association for statin drug use and local disease to a relative risk of 1.0 because that is compatible with the summary point estimate that we calculated using inverse variance weighting from all of the published studies [1–17]. We set the prevalence of statin use to 10% [1], assuming that men did not change their use status over time, and varied the percentage of statins users who underwent

PSA screening from 0 – 100%. We assumed an annual prostate cancer incidence rate of 1%, based on annual prostate cancer incidence rates from the Surveillance, Epidemiology, and End Results program for men ages 60–74 years; [19] this rate is a weighted average of risk across screened and unscreened men. Based on the Behavioral Risk Factor Surveillance System data on screening during the past two years, [20], we assumed that 65% of the men in the US were receiving screening. Based on preliminary results from the European Randomized Study of Screening for Prostate Cancer (ERSPC), we assumed a risk of prostate cancer diagnosis in PSA-screened men twice that in unscreened men. [21] We assumed an advanced stage at diagnosis in 20% and 40% of cases in screened and unscreened men, respectively. Data from SEER indicated that from 1999–2006 20% of cases of prostate cancer were regional, distant, or unstaged at diagnosis [22], and that from 1983 – 1987, prior to the PSA era, approximately 40% of cases of prostate cancer were regional, distant, or unstaged at diagnosis. [23] We assumed that in men not undergoing PSA screening, the stage distribution would be similar to that in the pre-PSA era (40%), and that in men undergoing PSA screening, the stage distribution would be similar to that during the PSA era (20%). These assumptions are summarized in Figure 3.

To determine the conditions under which extensive bias might be produced, we conducted smaller simulations (10 datasets with 100,000 men per dataset) varying the prevalence of statin use (from 10 to 40% to capture the range of prevalence of statin use across the follow-up period in published cohort studies [1,3]), the prevalence of prostate cancer (from 1 to 40%), and the proportion of advanced stage at diagnosis by PSA screening status (0–100% in each group).

Generation of Simulated Datasets

In simulating each dataset, we first generated 100,000 observations for a given joint distribution of statin use and PSA screening. We then generated the risks (i.e. probabilities) of no prostate cancer, localized prostate cancer, and advanced prostate cancer based on each observation's statin drug use and PSA screening status assuming an underlying polytomous logistic model. The probabilities were calculated using the assumptions discussed in the previous section; see appendix 1 for details on mathematical calculations. Once the probabilities were calculated for each observation using the previously generated PSA and statin use information, they were used to generate the outcome for each simulated observation in the dataset. All simulations and analyses were conducted using SAS v 9.1.3 (SAS Institute, Cary, NC) on a linux cluster of dual-core AMD opteron CPUs.

Calculation of Observed Simulated Associations (RR_{obs})

For each dataset, we modeled the association between statin drug use and total, localized, and advanced prostate cancer using logistic regression omitting the regression term for PSA that was used to generate the simulated data. We then averaged the β coefficient for statin drug use for all 3,000 of the simulated datasets and exponentiated it to obtain RR_{obs} . Although we estimated the odds ratio (OR) rather than the true risk ratio (RR), the odds ratio is a good estimate of the relative risk (RR) when the risk of the outcome is <10% (we assumed 1%). Therefore, throughout, we refer to the measure of association as the RR.

Results

The association between statin drug use and both localized and total prostate cancer varied with the percentage of men who both used a statin drug and underwent regular PSA screening (Figures 4a-4c). As this percentage increased, the RR_{obs} for both localized and total prostate cancer increased, biasing the association upward from the true null association. This bias was stronger in the simulation assuming a lower prevalence of regular PSA

screening in the population (Figures 4a-4c). However, the RR_{obs} was very close to the true RR for the association between statin drug use and advanced prostate cancer across the range of percent of men who both used a statin drug and underwent regular PSA screening (Figures 4a-4c). These results were similar when the incidence of prostate cancer was increased from 1 to 40% per year and when the prevalence of statin use was increased from 10 to 40% (data not shown).

We increased the probability that a case would be diagnosed at an advanced stage in men not undergoing PSA screening to 80% (as opposed to the previous assumption of 40%), and assumed a relatively high coincidence of statin drug use and PSA screening (80%). These assumptions introduced a slight bias in the association between statin drug use and advanced prostate cancer in that the RR_{obs} was lower than the true null RR of 1.0 (Table 1). Less bias was evident when it was assumed that a smaller proportion of men (<80%) were both using a statin drug and undergoing PSA screening (data not shown).

Discussion

In these simulated scenarios, we observed that detection bias due to medical practices that lead to a correlation between PSA screening and statin drug use is unlikely to explain the inverse association between statin use and advanced prostate cancer that has been observed in several prospective studies, [1–6] but it might explain the positive association between statin use and total prostate cancer that has been observed in some cohort and case-control studies. [3,4,7,15] The greatest bias in the association between statin use and total or localized prostate cancer was observed in simulations where a low prevalence of PSA screening was assumed. In the population with a low prevalence of PSA screening, when a high proportion of statin drug users are undergoing PSA screening, that means that a high proportion of men undergoing PSA screening are using a statin; in the population with a high prevalence of PSA screening, even when a high proportion of statin drug users are undergoing PSA screening, only a small proportion of men undergoing PSA screening are using a statin (Figure 5). Though counterintuitive, our study shows that the link between PSA screening and statin drug use may be stronger than previously thought in populations with a low prevalence of PSA screening.

The only simulated scenarios that produced a notable downward bias in the association between statin use and advanced prostate cancer were those that assumed a very high (80%) probability that a diagnosed cancer would be of an advanced stage in men not undergoing PSA screening (while simultaneously assuming a low (20%) probability that a diagnosed cancer would be of an advanced stage in men undergoing PSA screening). This is a higher probability than is likely to occur in reality; in the Health Professionals Follow-up Study, for example, the probability that a diagnosed prostate cancer would be of an advanced stage was 13% among men not undergoing PSA screening and 6% among men undergoing PSA screening; in the pre-PSA era in the US, only 40% of prostate cancer cases were diagnosed at an advanced stage, [23] and only 23% cases were diagnosed at an advanced stage in the placebo arm of the ERSPC. [24] Even using the very extreme probability of 80% (compared to the proportion of cases with advanced disease in the pre-PSA era, which was 40%), the biased RR_{obs} was still only 0.81, which is not as strong as some of the associations that have been reported in the literature, [1–3]. Because such extreme assumptions were necessary to produce this bias, it seems unlikely that detection bias fully explains the inverse associations between statin use and advanced prostate cancer that have been reported. Our best estimates of true values for the simulation parameters in the US population are as follows: prevalence of statin use=30% [25], 2-year prevalence of PSA screening=65% [20], annual cumulative incidence of prostate cancer = 1% [19], prevalence of advanced stage at diagnosis among men undergoing PSA screening = 20% [22], prevalence of advanced stage at diagnosis

among men not undergoing PSA screening = 40% [23]. Although the prevalence of PSA screening among statin users is unknown, it is likely somewhat greater than the 65% in the general population. Therefore, under these conditions that represent our best estimate of the real-world US population, we observed no downward bias in the association between statin use and advanced prostate cancer.

Our simulations are based on a simplification of complex real-world conditions, and we can only make inferences about these simulated scenarios. We stipulate that there may be other scenarios or mathematical models which could produce bias that would explain the results observed in the literature. However, we chose the range of values for the parameters of our simulation to be as close to contemporary reality as possible. The fact that notable bias is not produced until the assumed parameters are distorted far from reality indicates that the RR_{obs} is not highly sensitive to changes in these parameters.

Conclusions

Under the scenarios and assumptions we used, this simulation suggests that detection bias due to medical care practices that lead to a correlation between PSA screening and statin drug use is unlikely to explain the inverse association observed between statin use and advanced prostate cancer in some US and European cohorts, but could account for the positive association for total prostate cancer that has been reported in some studies.

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Appendix 1: Example of probability calculations

Note: Values marked with an asterisk (*) are varied in some simulation scenarios. The values used here for illustration may differ from the actual values used in some simulated scenarios discussed in the text.

Background calculations and assumptions

1%* = annual prostate cancer incidence rate

x = incidence of prostate cancer | no PSA screening

y = incidence of prostate cancer | PSA screening

y = 2x

60% of men undergo screening

0.01 = .4x + .6y

0.01 = .4x + 1.2x

x = 0.00625

y = 0.0125

assumed: P(advanced | prostate cancer and PSA screening) = 0.2*

P(advanced | prostate cancer and no PSA screening) = 0.4*

therefore:

P(localized | prostate cancer and PSA screening) = 0.8*

P(localized | prostate cancer and no PSA screening) = 0.6*

RR of localized prostate cancer for statin drug use = 1.0

RR of advanced prostate cancer for statin drug use = 0.75*

OR ≈ RR

Calculations for Localized Prostate Cancer

α_1 = ln(odds of localized prostate cancer among men who do not use statins and who do not undergo PSA screening)

$$\alpha_1 = \ln \left(\frac{P(\text{localized prostate cancer} | \text{no statin, no PSA screening})}{1 - P(\text{localized prostate cancer} | \text{no statin, no PSA screening})} \right)$$

$$\alpha_1 = \ln \left(\frac{P(\text{localized} | \text{prostate cancer and no PSA screening}) * (\text{incidence of prostate cancer} | \text{no PSA screening})}{1 - [P(\text{localized} | \text{prostate cancer and no PSA screening}) * (\text{incidence of prostate cancer} | \text{no PSA screening})]} \right)$$

$$\alpha_1 = \ln \left(\frac{0.6 * 0.00625}{1 - (0.6 * 0.00625)} \right)$$

$$\alpha_1 \approx -5.58$$

β_1 = ln (true odds ratio for the association of statin drug use and localized prostate cancer)

$$\beta_1 = \ln(1.0)$$

$$\beta_1 = 0$$

$$\gamma_1 = \ln \left(\frac{\text{odds of localized prostate cancer|PSA screening}}{\text{odds of localized prostate cancer|no PSA screening}} \right)$$

$$\gamma_1 = \ln \left(\frac{P(\text{localized|PSA screening}) / [1 - P(\text{localized|PSA screening})]}{P(\text{localized|no PSA screening}) / [1 - P(\text{localized|no PSA screening})]} \right)$$

$$\gamma_1 = \ln \left(\frac{0.8 * 0.0125 / (1 - 0.8 * 0.0125)}{0.6 * 0.00625 / (1 - 0.6 * 0.00625)} \right)$$

$$\gamma_1 \approx 0.99$$

Calculations for Advanced Prostate Cancer

α_2 = ln(odds of advanced prostate cancer among men who do not use statins and who do not undergo PSA screening)

$$\alpha_2 = \ln \left(\frac{P(\text{advanced prostate cancer|no statin, no PSA screening})}{1 - P(\text{advanced prostate cancer|no statin, no PSA screening})} \right)$$

$$\alpha_2 = \ln \left(\frac{P(\text{advanced|prostate cancer and no PSA screening}) * (\text{incidence of prostate cancer |no PSA screening})}{1 - [P(\text{advanced|prostate cancer and no PSA screening}) * (\text{incidence of prostate cancer |no PSA screening})]} \right)$$

$$\alpha_2 = \ln \left(\frac{0.4 * 0.00625}{1 - (0.4 * 0.00625)} \right)$$

$$\alpha_2 \approx -5.99$$

β_2 = ln (true odds ratio for the association of statin drug use and advanced prostate cancer)

$$\beta_2 = \ln (0.75)$$

$$\beta_2 \approx -0.29$$

$$\gamma_2 = \ln \left(\frac{\text{odds of advanced prostate cancer|PSA screening}}{\text{odds of advanced prostate cancer|no PSA screening}} \right)$$

$$\gamma_2 = \ln \left(\frac{P(\text{advanced|PSA screening}) / [1 - P(\text{advanced|PSA screening})]}{P(\text{advanced|no PSA screening}) / [1 - P(\text{advanced|no PSA screening})]} \right)$$

$$\gamma_2 = \ln \left(\frac{0.2 * 0.0125 / (1 - 0.2 * 0.0125)}{0.4 * 0.00625 / (1 - 0.4 * 0.00625)} \right)$$

$$\gamma_2 \approx -0.00003$$

Probability Calculations

- P_0 = probability of no prostate cancer
- P_1 = probability of localized prostate cancer
- P_2 = probability of advanced prostate cancer

For those taking a statin and undergoing regular PSA screening:

$$P_0 = \frac{1}{[1 + \exp(\alpha_1 + \beta_1 \text{ statin} + \gamma_1 \text{ PSA})] + \exp(\alpha_2 + \beta_2 \text{ statin} + \gamma_2 \text{ PSA})}$$

$$P_0 \approx \frac{1}{[1 + \exp(-5.58 + 0 * 1 + 0.99 * 1)]}$$

$$P_0 \approx 0.99$$

$$P_1 = \frac{\exp(\alpha_1 + \beta_1 \text{ statin} + \gamma_1 \text{ PSA})}{[1 + \exp(\alpha_1 + \beta_1 \text{ statin} + \gamma_1 \text{ PSA})] + \exp(\alpha_2 + \beta_2 \text{ statin} + \gamma_2 \text{ PSA})}$$

$$P_1 \approx \frac{\exp(-5.58 + 0 * 1 + 0.99 * 1)}{[1 + \exp(-5.58 + 0 * 1 + 0.99 * 1)] + \exp(-5.99 - 0.29 * 1 - 0.00003 * 1)}$$

$$P_1 \approx 0.01$$

$$P_2 = \frac{\exp(\alpha_2 + \beta_2 \text{ statin} + \gamma_2 \text{ PSA})}{[1 + \exp(\alpha_1 + \beta_1 \text{ statin} + \gamma_1 \text{ PSA})] + \exp(\alpha_2 + \beta_2 \text{ statin} + \gamma_2 \text{ PSA})}$$

$$P_2 \approx \frac{\exp(-5.99 - 0.29 * 1 - 0.00003 * 1)}{[1 + \exp(-5.58 + 0 * 1 + 0.99 * 1)] + \exp(-5.99 - 0.29 * 1 - 0.00003 * 1)}$$

$$P_2 \approx 0.002$$

Table 1: Early Stage Prostate Cancer vs. None

	Prostate Cancer		
	Early Stage	None	
Statin Yes	A	b	N ₁
Statin No	c	d	N ₀

$$\text{Relative Risk}_{\text{early}} = \frac{\mathbf{A}/N_1}{c/N_0} = \uparrow$$

Table 2: Advanced Stage Prostate Cancer vs. None

	Prostate Cancer		
	Advanced Stage	None	
Statin Yes	a	b	N ₁
Statin No	C	d	N ₀

$$\text{Relative Risk}_{\text{advanced}} = \frac{a/N_1}{\mathbf{C}/N_0} = \downarrow$$

Figure 1.

Men undergo regular screening for elevated PSA and cholesterol. Men who undergo regular PSA screening are more likely to be diagnosed with early stage prostate cancer and are less likely to be diagnosed with advanced stage prostate cancer. Men who undergo cholesterol screening are more likely to be prescribed a statin drug. Therefore, in Table 1 below, the A cell is overrepresented (depicted as a large, capital “A”), and in Table 2 below, the C cell is overrepresented (depicted as a large, capital “C”).

Figure 2.
Simulated Closed Cohort for Evaluating Detection Bias as an Explanation for the Inverse Association Between Statin Drug Use and Advanced Prostate Cancer

Figure 3. Assumptions* Used in the Simulations for Evaluating Detection Bias as an Explanation for the Inverse Association Between Statin Drug Use and Advanced Prostate Cancer

Figure 4.

Figure 4a. Observed Relative Risks (RR_{obs}) for the Association of Statin Use with Prostate Cancer When the True $RR = 1.0$

Figure 4b: Observed Relative Risks (RR_{obs}) for the Association of Statin Use with Prostate Cancer When the True $RR = 0.75$

Figure 4c: Observed Relative Risks (RR_{obs}) for the Association of Statin Use with Prostate Cancer When the True $RR = 0.5$

Figure 5.
Statin Drug Use and PSA Screening in Two Populations

RR_{obs} ** for the Association of Statin Drug Use with Advanced Prostate Cancer Varying the Probability that a Cancer is Diagnosed at an Advanced Stage

Table 1

		P(Advanced) no PSA Screening			
		0.2	0.4	0.6	0.8
P(Advanced) PSA Screening	0.2	1.10	0.90	0.98	0.81 *
	0.4	1.10	1.11	1.03	1.04
	0.6	1.29 *	1.19 *	1.06	1.13 *
	0.8	1.14 *	1.11 *	1.14 *	1.08

* $p < 0.05$

** Based on 10 datasets of 100,000 observations each. Assuming 80% of statin users are undergoing PSA screening. Assuming the true RR for the association of statin drug use with advanced prostate cancer is 1.0.