Reviewer's report

Title: Exposure to statins and risk of common cancers: a series of nested case-control studies

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Reviewer: Denise Boudreau

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Statins are commonly prescribed and it is important to understand their safety with respect to cancer. Numerous studies evaluated the association between statins and various site specific cancers and overall cancer risk. Results are mainly inconclusive but evidence is accumulating that statins may reduce aggressive prostate cancer risk. This study adds to the existing body of literature. Few studies have evaluated multiple site specific cancers within one population. This is a strength of the current study. The paper is well written and the methods appear rigorous. However, I found minor and a few major limitations as noted below as well as some suggestions for improving the study manuscript.

Discretionary Revisions

1. The paragraph on statin dose is not necessary in my opinion. I think it can be summarized in 1 sentence and then referenced.

2. It would be nice to know the overlap of cancer cases even if just by number and not site. Maybe a sentence or two about % with 2 and 3+ cancer cases detected during the study period.

Minor Essential Revisions

3. The authors do not seem to give enough acknowledgment to the fact that there are many mechanisms proposed for how statins may reduce cancer risk and progression in numerous cancer cells. More references and mention of a few more of the proposed mechanisms is needed in paragraph 2.

4. Results of the clinical trials is summarized well but there is no mention of the observational studies in this area. RCT were not powered to evaluate cancer as an outcome. Observational studies are strong in this area because confounding by indication is less of an issue. A few at least deserve mention in the background especially since the study under review is an observational study.

5. The authors should be clear in their statement of purpose that they are evaluating incident cancers.

6. More information is needed about the QResearch database regarding medications and cancer. For example, 1) Authors should be clear that these are dispensings and not just scripts ordered. Any validation work on completeness of pharmacy records? Are OTC meds included as well since NSAIDS and aspirin are often purchased OTC. 2) Do oncology records always make it into the
general practice database? Again, any info on completeness is welcome with regards to case ascertainment. 3) Is there information on cancer screening (e.g., mammography, PSA testing, colonoscopy)? These may be important in evaluating any detection bias as noted below.

7. It appears that both cases and controls with prior mastectomy regardless of breast cancer diagnosis were excluded from later in the manuscript but it is not clear in the exclusions as only controls are mentioned.

8. I find the exclusion section on secondary cancers confusing because it is stated earlier that the cases were the first record of any cancer. How many secondary cancers were there and how was this determined? What was done with second primaries and recurrences – could they determine them, etc.? Making it clear that incident cancers are the outcome would be helpful.

9. The Townsend score should be better explained. Is this a measure of SES?

10. The first 2 paragraphs repeat the results. A dive into why they found some increases in cancer risk when other observational studies find either no increased risk or decreased risk would be a better use of space.

11. There are numerous trials of statins as chemopreventive agents in clinicaltrials.gov. This should at least be mentioned since it speaks to the strong evidence for statins in chemoprevention – yet this study finds increases in risk.

12. Any cancer is not specific enough of an endpoint and this should be noted in the discussion when these results are mentioned. This is a major limitation of the meta-analyses as well that the authors mention. It is reassuring but not specific enough to draw any definitive conclusions and site-specific cancers are really what is of interest.

13. Looking at multiple cancers within the same population is a strength and should be noted so in the discussion section.

Major Compulsory Revisions

14. Lung cancer as an outcome is not really of interest due to the strong impact of smoking. If lung cancer is kept in the paper, results should be stratified by smoking status. It is odd that adjustment only moved the point estimate slightly. It implies there may be residual confounding or effect modification.

15. How were confounders determined? 10% rule, a priori, stepwise? What is the rationale behind adjusting for the same confounders for each cancer? Many of the co-morbidities are not necessarily risk factors for the cancers. The authors include medications associated with increased risk of cancer but no reference is provided to justify this statement. I know of no studies that find an increased risk with non-statin lipid lowering medications. Similarly, they do not include medications associated with a decreased risk in cancer such as metformin and bisphosphonate? I find the selection of confounders very arbitrary. An a priori approach should be taken that makes biologic sense and is backed by literature in the area.

16. Patients with colitis and crohn’s disease should be excluded from the CRC model. It is a different disease pathway and their risk is much higher than the
general population.

17. There is no adjustment or mention of screening. It is very likely that cancer screening differs between statin and non-statin users. There are a few articles in the literature linking statins to healthy user bias. Statin users, for example, are more likely to undergo mammography screening than non-users. Similar may be expected for PSA testing and colonoscopies. This should be explored if the data are available or at least mentioned and referenced as a potential limitation.

18. No power calculations were done. The authors state that none were needed because they took all cases but this is not adequate. Only cancers with adequate power should be included as outcomes in the site specific analyses. All cancers can be included in the “any” analysis but the site-specific should be limited to cancers with enough cases to detect an OR of clinical significance. Some of these cancers are rare and I am surprised the models did not crash for these small cancer sites.

19. There is nothing to indicate that the mechanisms of action for how statins may influence cancer risk differ by gender. The authors state that they analyzed men and women separately because the prevalence of statin use is different. This is not an adequate reason especially when CVD is unlikely related to cancer risk. The results should be combined and sex adjusted for the main analyses except for sites that are gender specific such as breast and prostate. They can then mention where the results were different by gender in the text as part of secondary analyses. This will also help power calculations done to decide what cancers to include.

20. There is so much literature published on statins and risk of cancer? The authors mention very few of these studies. It is almost as if they are unaware of the huge body of literature. At least some of these studies or reviews of the studies should be acknowledged and referenced.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests