Author’s response to reviews

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

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Version: 2 Date: 30 August 2011

Author’s response to reviews:

Dear Editor,

We would like to thank the reviewers for their profound work on our paper. Please find the details of our revision below:

General notes

Major revision:
We have rerun the analyses combining both genders and considered only 10 commoner cancers including haematological malignancies as a type of cancer. Previous findings of an association between prolonged statin use and increased risks of bladder and colorectal cancers in men were similar to the results of the current analyses on the combined sample. We have had more power to show the association between prolonged statin use and risk of lung cancer. The previously shown association between reduced risk of leukaemia in men and statin use was confirmed in the combined analysis and demonstrated a similar association for other haematological malignancies.

Minor revision:
We have recalculated dose of statins not as the last prescribed but as median dose across the observation time period (i.e. 13 to 72 months prior the index date or 13 to 120 months for the additional analysis).
We have changed Figure 1 to address statin use for more than a year, not at least 2 prescriptions over the study period as in the previous version.

Reviewer 1

1. The paragraph on statin dose is not necessary in my opinion. I think it can be summarized in 1 sentence and then referenced.
   This has been done (Page 7 paragraph 3).
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.
Unfortunately we don’t have this information as we extracted only the first ever diagnosis of cancer and all records before that.

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 of the proposed mechanisms is needed in paragraph 2.

We have added this information to the Introduction (Page 3 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.

We have rewritten that part of Introduction, mentioning RCTs as well as adding additional information on observational studies (Page 4, paragraph 2).

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

We have rephrased the last sentence in the Introduction to make this clear.

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.

1) We say in the 1st paragraph in Methods that the database contains information on prescriptions (we have just added ‘including repeat prescriptions’). We mention in the Discussion under limitations that we analysed information only on drug prescriptions and not the actual use. We have also noted as another limitation of the study the lack of information on OTC statins although this would have affected only younger patients and a small part of the study. (Page 19 paragraph 3)

2) We have added a reference in the 1st paragraph of Methods about the validation of QResearch. More information can also be found in the link to QResearch provided (Page 5 paragraph 1).

3) We did not use this information as it wasn’t in our protocol and we aren’t sure how complete it would be since mammography (for example) is organised outside the practice. Otherwise we would have used it and reported it. We have noted this in the paper. (Page 18 paragraph 4)

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.
We have clarified this, it is ‘cases and controls’. (Page 5 paragraph 3)

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.

We say that the cases were the first record of cancer during the study period. They might have had cancer diagnosed before but we do not have an access to this information therefore we had to exclude cases with secondary cancers. (Page 5 paragraphs 2-3)

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

Yes. We have added that it is ‘measure of socio-economic status’. (Page 8 paragraph 2)

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.

We have removed the 2nd paragraph and added references to observational studies (pages 16-17).

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.

We haven’t been able to find any which relate to statins as chemopreventive for patients with no history of cancer. There are numerous trials looking at effect of statins on remission of cancer but none of them recruited healthy participants.

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.

We have noted this in Discussion (page 16 paragraph 2).

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

We have added this to Strengths (page 18 paragraph 2).

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.

The proportion of ever-smoker patients was much higher in cases (66%) than in controls (36%). The observations were not matched by smoking status, so stratifying by smoking would result in removing a significant number of observations from the analysis due to absence of a matched case or control. For
example, for ever-smokers in lung cancer data, 30% of cases don’t have matched controls. We have tried to address this issue better in the paper (Results page 14, paragraph 2, Discussion page 17 paragraph 3).

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.

We had determined confounders a priori. We have now added the references for each confounder (Page 8, paragraph 2). We had provided the references for NSAIDs but not for non-statin lipid-lowering drugs. We have now removed those from the analysis (and the results were not noticeably affected). Although we did not extract information on metformin and bisphosphonates, we have adjusted for diabetes.

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.

We adjusted for ulcerative colitis and Crohn’s disease. Excluding those did not noticeably change the results.

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.

We have added the unavailability of cancer screening tests to the limitations (page 19, paragraph 2).

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.

We have added post-hoc power calculations (Page 9, paragraph 1).

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.

We have rerun the analysis on both genders combining the results as it was suggested. The effect of statin on any cancer site has stayed not statistically significant. Associations between prolonged (more than 4 years) use of statin and increased risks of colorectal and bladder cancers are significant on the combined sample compared to men only effect in the previous analysis. Increased risk of lung cancer is significantly associated with long-term statin use in the current analysis. The previously found association between statin use and reduced risk of leukaemia in men has been extended to all haematological malignancies in men and women combined.

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.

Yes, there is a vast amount of the literature so we have had to mention only key publications limiting ourselves to studies where exposure to statins was for more than 4 years. We have added the most recent publications issued after our first submission (Page 3, paragraph 2) and more observational studies to the Discussion (Page 16 paragraph 3 to Page 17 paragraph 4).

Reviewer 2

1. Exposure variables: why was the minimum number of statin prescriptions set at 2 to be considered a statin user? This seems potentially low over a 60 month period to make clinically meaningful associations with cancer development if a patient were only taking a statin for 2/60 months (3% of the time).

We have added an analysis of statin use for more than a year, Figure 1 now shows the odds ratios for use for more than a year.

2. Statin Exposure: number of prescriptions and months on statin: may want to state in previous section the length of available prescriptions (i.e. does a prescription for a statin imply a 30 day course, or does it imply more than 30 days in some cases, or does it imply the time that the prescription remains active and is available for refills?)

For approximately 60% of prescriptions the duration is 28-30 days. For another 20-25% it’s for 56-60 days. The variability of length is the reason we decided to assess the cumulative duration rather than number of scripts.

Minor Essential Revisions:
1. Cyclo-oxygenase misspelled in abstract
   Corrected.
I hope we have addressed all the issues and you will find the paper improved.

Yours sincerely

Yana Vinogradova