Author’s response to reviews

Title: Cardiovascular medication use and risks of colon cancer recurrences and additional cancer events: a cohort study

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Author’s response to reviews:

Joshua Mammen, MD, PhD
Editor, BMC Cancer

February 15, 2019

Dear Dr. Mammen,

Thank you for considering the original research article “Cardiovascular medication use and risks of colon cancer recurrences and additional cancer events” for publication in BMC Cancer. We
have revised the manuscript according to the reviewers’ suggestions and hope that it is now acceptable for publication. A point-by-point response is included at the end of this letter.

Potential competing interests are as follows: Onchee Yu reports receiving funding as a biostatistician from a research grant awarded to Kaiser Permanente Washington Health Research Institute from Bayer. Monica Fujii reports receiving funding from a research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward. Denise Boudreau reports receiving funding from research contracts awarded to Kaiser Permanente Washington Health Research Institute from Allergan, BioDelivery Sciences, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Janssen, Mallinckrodt, Pernix, Pfizer, Purdue, and West-Ward. All other authors declare they have no competing interests.

This manuscript has not been published and is not under consideration for publication elsewhere. All authors have approved the manuscript for submission.

Sincerely,

Erin Bowles, MPH
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Point-by-point response:

Elizabeth Dennett (Reviewer 1): Comprehensive study that helps with decision making around cardiac medications in the face of previous contradictory study result.

I think this is a good study and the results are well presented with appropriate limitations identified.

It is however not clear to me why Hispanic ethnicity is given its own category in all the tables apart from the Race category. In addition w.r.t to race - white and black are not races they are skin colours. Surely the appropriate categories are African American and American European? At the very least it would help to explain why Hispanic has a completely separate category to race.

Response: The United States Federal Data Standards (https://nces.ed.gov/programs/handbook/data/pdf/Appendix_A.pdf) include Hispanic ethnicity as a separate category to race. This standard is followed in reporting for National Institutes of Health grants (which funded this study) and in national Surveillance Epidemiology and End Results (SEER) data collection. Collecting and reporting these data is critical to understanding
why racial and ethnic minorities (including Hispanics) experience poorer health outcomes, including higher rates of cancer and cancer recurrence. The race and ethnicity categories we show in this manuscript are standard; therefore, we have maintained the categories as originally presented in the manuscript.

Ming Jen Chen (Reviewer 2): Cardiovascular medication use and risks of colon cancer recurrences and additional cancer events: a cohort study by Bowles EJ et al. Cancer patients often deal with comorbidities after their treatment, such as cardiovascular disease, that need treatment in addition to their cancer. Statin and antihypertensive use is common among colon cancer survivors and their treatments may impact their risk of recurrence and overall mortality. Therefore, this study is conducted to understand the long-term risks and benefits of these drugs in this population. Although this article is quite interesting and well written, there are some concerns on the methodology which need to be further clarified.

Comments to the authors:

1. As the authors mentioned, medications such as statins and antihypertensives may be commonly used among colon cancer survivors. The correlation or causation between the medication and cancer (colon cancer vs other cancer type) is still unclear and need to be further clarified. Without good explanation for the causation, the null results suggesting these medications do not appear to impact seems to less clinical relevant.

Response: As noted in the introduction, statins have been shown in many studies to decrease cell proliferation (references 11-19), which has the potential to reduce colon cancer recurrence. The relationship between antihypertensives and colon cancer recurrence may differ by class. ACE inhibitors, ARBs, and beta blockers have been shown to limit tumor cell growth, which may also reduce recurrence risk (references 22-26). However, calcium channel blockers and thiazide diuretics may increase risk through cellular pathways that prevent cell death or increase insulin resistance (references 30-33). Because cancer is marked by uncontrolled cell growth and reduced cell death, regardless of cancer type, the mechanisms should apply to any cancer type and cancer recurrence. However, it is important to examine these associations epidemiologically in population-based studies in addition to laboratory-based studies of cellular mechanisms. To acknowledge that causal mechanisms in this area are limited, we have added a statement to the conclusions on page 15, lines 18-22:

“Despite laboratory studies suggesting cellular mechanisms for CVD medications to either promote or inhibit cell growth, and subsequently increase or decrease cancer risk, we could not confirm these results in our study. This highlights the importance of conducting both laboratory and epidemiological studies because cellular mechanisms do not always translate directly into population-based studies.”
2. The mechanism or pathway for colon cancer recurrence and other various type primary cancers may be quite different. The second outcome of interest in this included any cancer event, defined by a colon cancer recurrence, second primary colon cancer, recurrence of another cancer, or new primary cancer at any site. There is a diversity of outcomes measurement which might contribute clinical heterogeneities and the authors may hard to interpret it.

Response: We agree with the reviewer that the pathway for colon cancer recurrence development may be very different than the pathway for any subsequent cancer development – and different subsequent cancer types may be very different. We did not have statistical power to examine different types of second primary cancer development and have acknowledged this as a limitation on page 15, lines 3-6:

“It is possible that heterogeneity in development of different types of second primary cancers may be masking any association between CVD medications and second cancer events. However, we did not have sufficient numbers of different types of other cancers to examine these associations individually.”

3. Though the authors listed some limitations, the quality review of the studies is poorly conducted with hidden information and confounding factors (such as diabetes and aspirin use) including the judgement of the degree of risk of bias. Besides, there is a high portion of the measurement failure among the included studies (16%). It might not be able to pool the biased data and give a simple conclusion.

Response: Our manuscript was not a systematic review, thus we did not report a quality review of any studies. Measurement failure and pooling of studies do not apply in this case. The 16% the reviewer refers to is the proportion of people who disenrolled from one of the health systems during the study, potentially limiting follow-up. However, our analyses censored subjects at disenrollment, and would not have counted any follow-up time after that point.