Author's response to reviews

Title: Cancer risk among elderly persons with end-stage renal disease: a population-based case-control study

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Version: 2 Date: 14 June 2012

Author's response to reviews: see over
June 14, 2012

*BMC Nephrology Journal*

Dear Dr Hayley Henderson,

Thank you for inviting us to revise and resubmit our manuscript entitled “Cancer risk among elderly persons with end-stage renal disease: a population-based case-control study”. In the enclosed response to reviewers, we addressed each reviewer’s comments point by point. The changes are highlighted in the attached manuscript. Please let me know if you have any questions.

Sincerely,

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Response to reviewers

Reviewer: Micah L Thorp
Reviewer's report:
The study by Shebl et.al. is a case control study examining the risk of ESRD among patients with cancer. Cases were extracted from the SEER data system and controls from a Medicare population. ESRD cases were identified using ICD-9 and CPT codes. The study is well written and produces some novel information. I have only a few criticisms:

Major revision:
1- The authors suggest they are examining the relationship between ESRD and cancer. Strictly speaking this is incorrect. Their study examines the relationship between dialysis and cancer. The codes they use to identify “ESRD” are exclusively dialysis codes. ESRD includes patients on dialysis and those with CKD stage 5. Some entities include patients who have received a renal allograft in their “ESRD” definition, though this is not the norm. In either case, the nomenclature needs to be changed throughout the paper. Additionally, I didn’t see any peritoneal dialysis codes (at least the ones that are commonly used) though the revenue center codes may pick this up.

Response: We have used dialysis codes because the Medicare lacked specific ESRD codes in the study time frame. Specifically, the ICD-9 diagnosis code 585 for “chronic kidney disease” was available, but not the more specific code 585.6 for ESRD. Therefore, we relied on dialysis codes. In order to ensure that the individuals had ESRD, we required that dialysis claims be present for each of the 3 months prior to selection. Using this approach, we believe that most of the selected people had ESRD, although, there is slight probability of including less chronic cases which might attenuate our findings. To address the reviewer’s concern, we have added this information to the Methods and the Discussion as follows:

Methods, page 7: “For each case and control subject, we defined ESRD to be present based on Medicare claims for chronic dialysis care that was consistent with ESRD. We used this ascertainment tactic because there were no ICD-9 diagnosis codes in the Medicare claims files specific to ESRD.”

Discussion, page 17: “However, because we used dialysis claims to identify people with ESRD, we may have inadvertently included some people with less severe kidney disease.”

As regards peritoneal dialysis, this was captured by procedure codes 90925 (ESRD service for full month), 90945-90947 (dialysis [other than hemodialysis] service with physician evaluation), and 90966 (services for home dialysis), and revenue center codes 083x (Peritoneal Dialysis - Outpatient or Home), 084x (Continuous Ambulatory Peritoneal Dialysis (CAPD) - Outpatient or Home), and 085x (Continuous Cycling Peritoneal Dialysis (CCPD) - Outpatient or Home).
Minor revision:

2- I’m also not aware of the effect of Medicare Advantage patients in this mix – it may have an effect on billing codes (insurers are given a lump sum for a large population of Medicare patients – and Medicare claims are not made in the same fashion). Whether or not this effect is present should be mentioned in the paper.

Response: Medicare Advantage (or part C of Medicare) is the HMO component of Medicare, and as the reviewer indicates, HMOs receive capitated payments for care and there are no billing codes available. Therefore, we required cases and controls to have at least 12 months of Part A, Part B, non-HMO Medicare coverage (i.e., excluding Medicare Advantage) prior to selection. While some cases and controls could have had some prior Medicare Advantage coverage, they all thus had at least 12 months for which claims data were available.

3- A portion of the dialysis patients included likely had prior renal transplantation. The numbers may not be large, but they are at high risk for cancer, particularly b-cell lymphomas (which would explain the high rates of small intestinal cancers).

Response: We agree with the reviewer that individuals with a kidney transplant could affect estimates of cancer risk. However, we have already excluded kidney recipients from the study, as we stated in the Methods section, page 6 as follows:

“We excluded cancer cases from the analysis if they had a prior Medicare claim indicating a history of organ transplant or were ever infected with human immunodeficiency virus, to assure that cases were not due to known causes of immunosuppression.”

“Following selection of 100,000 controls, we excluded individuals if they had a prior Medicare claim of history of organ transplant or were ever infected with human immunodeficiency virus.”

4- In addition the majority of patient on dialysis receive erythropoietin – which appears to have significant carcinogenic risks. It would be appropriate to add this to the discussion.

Response: As suggested by the reviewer we added the following statement to the Discussion (page 13): “Individuals with ESRD commonly receive erythropoietin [24] for treatment of anemia, which might be implicated in carcinogenesis and could potentially explain some of the observed excess cancer risk among individuals with ESRD.”
Reviewer: Kuan-Yu Hung

Reviewer's report:
The value of this work may be the screening awareness of associated malignancy in ESRD patients. But as shown in Table 2, it's too diverse to have a screening suggestion to physicians caring these ESRD patients.

1. In order to be more focusing, can we just enroll GU-tract malignancy?, as these are biologically relevant and can possibly be explained by underlying immune dysfunction or else.

Response: The motivation of this work was to study all malignancies comprehensively, and to take advantage of the SEER-Medicare database to study both common and rare cancers, without prior hypothesis of what type of cancer that might be increased. Therefore, we believe that the comprehensiveness is strength of our study. We would therefore propose to leave results for all cancers in the paper.

2. For those with multiple myeloma (MM), can we analyze further whether these patients have longer duration of MM? Can it be possible that it's the MM that leads to ESRD in these patients?

Response: The SEER database captures the date of MM diagnosis, but does not capture its duration. For a cancer like MM, the duration at diagnosis is probably short (i.e., a few months), although the precursor condition (monoclonal gammopathy of undetermined significance) could have been present for years. Of note, our latency analysis showed that individuals with shorter duration of dialysis had a higher risk of MM compared to individuals with longer duration of dialysis. This pattern implies that MM led to ESRD, as the reviewer suggests. We elaborated on this point in the Discussion page 14, as follows “In contrast, the strong increase in multiple myeloma risk in the first 1-2 years after ESRD diagnosis, and declining risk over longer time intervals, could be attributed to reverse causality, such that multiple myeloma leads to renal failure. This situation could arise if multiple myeloma was undiagnosed at initiation of dialysis, or if the diagnosis date is in error in the cancer registry due to delayed reporting. Maisonneuve et al. also noted the excess of multiple myeloma cases and likewise attributed this observation to prevalent cases [5].”

3. For prostate cancer (Table 3), do you suggest that ESRD patients receive PSA survey on a regular basis?, and the frequency? It's a clinically important and practical issue.

Response: Indeed, we do not advocate for increasing the PSA screening frequency among individuals with ESRD. Recent reviews of PSA screening have not supported its utility in the general population, and given the poor survival among men with ESRD, increasing the screening would likely not be cost effective. We emphasized this issue in the following two sections of the Discussion as follows:

Page 16: “However, we do not advocate for increasing the frequency of screening among men with ESRD. Recently the U.S. Preventive Services Task Force (USPSTF), opposed the use of
PSA for prostate cancer screening regardless of age because the harms overweigh the benefits [45]. Given, the overall poor survival of men with ESRD, PSA-based prostate cancer screening will not be of additional value.”

Pages 17-18: “Our results may help inform clinical decisions about cancer screening. Given the lower risk of prostate cancer in men with ESRD, and the lower life expectancy of these men relative to the general population there is no indication that men with ESRD should receive PSA testing. These findings also do not support more aggressive screening for other common cancers, because there was no increased risk for breast cancer, and only a modest increase in colon cancer risk. Similarly, others have suggested that in the circumstances of high morbidity and mortality from other diseases, screening for kidney cervical, colon, and breast cancers is less cost-effective than other health interventions in the ESRD population [47-49].
Reviewer: Germaine Wong

Reviewer's report:
1- Major compulsory revisions - Would expect authors to comment on the sample selection of the control.

Response: We previously included text in the Methods describing control selection. In response to the reviewer’s comment, we have rephrased this section (page 6) to clarify the control selection: “We randomly selected 100,000 controls from the 5% sample of Medicare beneficiaries living in SEER areas to match the total group of cancer cases. Specifically, controls were required, as of July 1 in the calendar year of selection, to be alive, free of any malignancy reported to SEER, and have at least 12 months of prior Part A, Part B, non-HMO Medicare coverage. From this eligible group, we then selected controls who were frequency matched to the entire group of cancer cases by individual calendar year of diagnosis, gender, and age in five categories (66-69, 70-74, 75-79, 80-84, 85-99 years). A subject could be selected as a control multiple times for cases in different calendar years and could later become a cancer case.”

2- Could the authors provide objective evidence of prostate cancer screening in patients with ESKD?

Response: We have added the percentage of PSA screening for prostate cancer among men with and without ESRD as follows, pages 11-12: “Among controls, men with ESRD were less likely than men without ESRD to have a claim for a PSA test in the one-year period prior to selection (24.1% vs. 35.5%, OR 0.58, 95% CI 0.43-0.78). Among prostate cancer cases, a claim for PSA testing was present in the year prior to diagnosis in 59.2% and 67.9% (OR 0.69, 95% CI 0.55-0.85) of those with and without ESRD, respectively.”