Editor Comments:

Each of the scientific reviewers have raised concerns with regard to the scientific validity of the analysis. Specifically reviewers 1 and 3 have raised serious concerns with regard to the direction, strength and validity of the associations between specific biopsy-proven glomerular disease diagnosis and the risk of cancer. Each of the reviewers concerns should be addressed in detail. Furthermore, the study would benefit from

1. Greater discourse on the temporal relationship of timing of biopsy and cancer incidence. Why is it that for some cancers, peak incidence occurs near the time of biopsy and fall thereafter? Is there a plausible biological basis to support the observed epidemiological trends? Is this all due to chance?

We have added “If one assumes that disease diagnosis time point is associated with disease severity and/or accelerating activity, the close temporal conjunction of the cancer and GN diagnoses suggest that any aetiological common agent is proportional to disease severity.” As we have emphasized, discussion of aetiology is speculative.

2. Greater discourse on the fact that the high prevalence of glomerular disease (GN) at time of biopsy among those with prevalent cancers is largely due to surveillance bias (greater intensity of investigation).

We beg to differ. While this is a very important factor, we do not believe that this can explain the entire difference. One of the major advantages of this study is that cancer incidence at some time before and after renal diagnosis is available, showing that overall cancer incidence, regardless of diagnosis time point is increased. The subject is discussed in paragraph 2 of the Discussion, and the conclusions nuanced as requested.

3. The inclusion of cancers prior to renal biopsy diagnosis adds an additional degree of complexity to the manuscript is it is unclear whether this represents a surveillance bias or
a true correlation. The authors may consider restricting the analysis to incident cancers detected after the diagnosis of GN at time of biopsy.

We feel that cancers prior to renal diagnosis are important. Particularly in the year before and after renal diagnosis, it may be fairly arbitrary whether the cancer diagnosis is made prior or subsequent to the renal diagnosis. We have therefore chosen to keep this analysis in the text.

4. More robust analysis of the associations of GN with the risk of cancer beyond the comparison of observed/expected incident rates. The lack of adjustment for potential confounders is a major limitation.

This is a major disadvantage of the study. The only available clinical information was the nephrological clinical diagnosis at biopsy, available for 78% of patients. The influence of these confounders are presented in paragraph 4 of the results, and discussed in paragraph 4 of the Discussion. The influence of age is very important; this is shown in Fig. 2 and Table 7.

5. Better description of the Results Section. There is a tremendous amount of data provided in text and in Tables/Figures that requires better organisation and a more tailored description for the casual reader. The authors should consider subheadings that would describe the primary results under sections of GN and Prevalent Cancer, GN and Cancer Incidence, and the relationship of specific GN diagnosis (and timing of biopsy) with cancer.

This has been done. To improve comprehension, significant values in Tables 1-3 are now shown in bold type, and figure 4 has been added.

6. More temperate language in the concluding sections (Page 7) is required. The conclusions appear speculative without a strong evidence from the reported results.

The recommendations have been modified, and are not as strong as before.

BMC Nephrology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Navin Jaipaul (Reviewer 1): This is a descriptive study of prevalent and incident cancer diagnoses observed in patients with biopsy-proven glomerulonephritis (GN) over a 20-year period, before and after the midpoint of GN diagnosis, extracted from two Danish renal biopsy registries and linked to cancer diagnoses in the Danish Cancer Registry. The authors report increase in cancer rates observed for most varieties of GN, particularly membranoproliferative GN in the older cohort over age 64. Due to their findings, the authors conclude that Nephrologists should consider expanding cancer screening for GN beyond the current standard practice for membranous nephropathy.
Several concerns necessitating major revisions:

1. While the study benefits from a large population in a well-established and validated cohort of patients, the cancer risk stratified by GN category is expressed by observed and expected rates rather than risk ratios which would be more clinically relevant measures.

The expression O/E is identical to the Risk Ratio. This has now been made clear.

2. Of particular concern relating to study validity are conflicting results which are inconsistent with other reported and well accepted associations of GN and cancer in the literature. The authors also point this out, but their explanations are not sufficiently convincing to reconcile the discrepancy.

The discussion on this topic has been considerably expanded. We are critical of previous associations, which are often based on small series, and do not take account of the fact that common cancer forms a priori will be overrepresented. The question arises whether a metaanalysis of published results would demonstrate statistically significant differences, but this is beyond the scope of this paper.

3. The study appears to lack adjustment for other factors which may contribute to the incident development of cancer in GN patients, such as treatment with immunosuppressive medications, comorbid conditions like HIV and Hepatitis C which lower immune tolerance, and advancing age. This residual confounding prevents evaluation for an independent association of GN with incident cancer diagnosis.

This is indeed a problem with this study. The question of immunosuppressive therapy is addressed in paragraph 2 of the discussion. We feel that the question of age has been sufficiently solved in our paper: age- and sex-specific rates are used for comparison to the general population, and the effect of age is shown in table 7.

4. Relevant baseline demographics of the study population have not been presented.

As this is a register study, only age and sex were available, as shown in Table 1. Most patients were Caucasian; this is now stated.

5. Due to these limitations, the study is not designed to determine incident cancer risk or screening indications for patients with GN and the conclusions are not supported by the data.

We beg to differ. This is the largest study on the subject, and thus one of the few studies permitting statistical analysis of the results. There is of course still the possibility of type 2 statistical errors, but this is unavoidable. We hope that we have been sufficiently cautious in our interpretation of the data.

6. Results may not be generalizable to other populations.
This is now stated.

Luc Frimat (Reviewer 2): The manuscript BMC-D-17-00429 by Heaf et al. Quantification of Cancer Risk in Glomerulonephritis, focus on the association between glomerulonephritis and cancer.

A first study has been conducted from 1985 to 1996, published in KI 2003 by Birkeland. The present study updates this cornerstone study. The database has continued prospectively for 30 years. It allows a detailed study of cancer incidence, with accurate measurement of risk. It provides important sources to improve patients’ care.

This nationwide registry study is a very well-conducted study. The precision of data, particularly definitions and exhaustivity, are crucial to the quality of this type of study. The present study fits these standards. The reference list looks exhaustive.

The authors should refer to Equator network recommendations for publications of observational studies (https://www.equator-network.org/library/).

A reference to the STROBE guidelines has been provided.

One concern is about definitions of glomerular disease. Notwithstanding, it does not fit exactly definitions used in the KDIGO guidelines published in KI in 2012 (KDIGO Clinical Practice Guideline for Glomerulonephritis volume 2 | issue 2 | JUNE 2012). A table facing Abbreviations used in the present study and KDIGO definitions should enhance the impact of the results.

This has been done. Where possible we have now used the KDIGO terminology. There are some discrepancies. Not all SNOMED diagnoses are used in the KDIGO guidelines. Most cases of endocapillary GN will be equivalent to KDIGO “Infection-related GN”.

Matthew Abramowitz (Reviewer 3): Heaf et al. examine the association of a variety of glomerulonephritis diagnoses with cancer both pre- and post-diagnosis. This is an important topic but it is not clear what conclusions can be drawn from this paper. While the authors mention a number of limitations, they are not sufficiently addressed. I have the following comments.

1. There are many comparisons made. Each table in the paper has 100-150 cells breaking down a total of 911 cancer cases. This is a tremendous amount of data, but it is difficult to draw conclusions about the association of any specific GN diagnosis with cancer, and especially with a specific type of cancer.

We agree that there is a lot of data. We feel that this is necessary, since we wish to fulfill two aims: to provide the most comprehensive description of cancer epidemiology in GN to date, and to give physicians documented guidelines for treatment. We have improve the appearance of Table 2 by highlighting significant figures.
(see reviewer 1, point 2). Our reading of our results and the literature on the subject seems to suggest that it is only in special circumstances (e.g. thymomas) possible to associate one GN diagnosis with one cancer form and vice versa. This is now discussed.

The involvement of time is also confusing and the directionality of the GN-cancer association is not entirely clear. It is unclear what the significance is of cancers diagnosed 5-10 years before the GN diagnosis.

The time intervals were chosen, since these data were available in NORDCAN. We were interested in time intervals before renal biopsy because an excess cancer risk long before renal biopsy, as seen for non-melanoma skin tumours, could have aetiological significance.

The authors do not address the possibility that certain cancers could have been incidental and only diagnosed because of increased surveillance after the GN diagnosis. It is also possible that some indolent GN diagnoses could have been made because of increased surveillance of cancer patients, with hematuria or proteinuria detected on a urinalysis.

We entirely agree. This is now made clear in the discussion.

2. The use of registry data is a significant limitation. Given the weight given to the GN diagnosis in these analyses, the kappa 0.61 for GN diagnosis is not reassuring.

This point about the disadvantage of epidemiological studies is well taken, and now mentioned in the text. A Kappa of 0.61 does not sound very impressive, but competes well with other diagnostic systems, particularly when a number of panel members are evaluating a number of different diagnoses. This study included only light microscopy evaluations; the real accuracy is probably higher since inclusion of immunopathology and electron microscopy (where indicated) is now routine.

The authors are also unable to account for the effects of immunosuppression on cancer risk after the GN diagnosis.

See reviewer 1, point 2. We agree that this is a disadvantage of this study. The problem is discussed in paragraphs 2 and 4 of the Discussion.

3. The authors give meaning to the differences between their current findings and of the prior study, but given the large number of comparisons, this may simply be due to chance.

We entirely agree. This is now stated.

Similarly, the sentence on page 7, line 32 - that finding associations only for some GNs and cancers argues against a coincidental association - is incorrect. This is to be expected given the many comparisons.

We entirely agree. This sentence has been deleted.
4. Given these limitations, the authors' recommendations for clinical care at the bottom of page 7 are too strong and are not justified by their data.

The recommendations have been modified, and are not as strong as before.