Author’s response to reviews

Title: The impact of cancer on diabetes outcomes.

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Author’s response to reviews:

Dear Editor

Thank you very much for having read and reflected upon our article so carefully, and thank you for the reviewers’ comprehensive comments. We have now worked thoroughly through the manuscript and revised it according to the comments.

We have attached a “clean version” of the manuscript: “Main Document_R1_clean”. The point-by-point answers to the reviewers are inserted in a copy of the reviewers’ comments below.

We look forward to hearing from you again.

On behalf of all authors.

Yours sincerely

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Reviewer reports:

Marco Gallo (Reviewer 1): The authors discuss the impact of a cancer diagnosis on the outcomes of diabetes management in the population-based cohort from the Diabetes Care in General Practice (DCGP) trial. In that trial patients with newly diagnosed type 2 diabetes were previously randomized to receive either structured personal diabetes care or routine care. The present analysis is a 19-year follow-up and post hoc observational analysis of the cohort. As stated by the Authors, while many studies describe how diabetes affects the incidence and mortality of cancer, studies on the impact of cancer on diabetes-related outcomes are rare. Results demonstrate that, compared to diabetes patients without cancer, patients with both diabetes and cancer had significantly increased all-cause and diabetes-related mortality, as well as an increased incidence of any diabetes-related endpoint and MI. Yet, diabetes patients with cancer benefitted from structured personal diabetes care as well as diabetes patients without cancer, to the same degree. As well acknowledged by the Authors, the results from this post hoc analysis of a RCT should be interpreted as observational, as the presence of cancer was not accounted for in the randomization procedure. In my opinion it is a well performed analysis and its population-based approach is one of its strengths. I only have a few comments and suggestions.

Minor Essential Revisions

1. The analysis examined only survived (and re-examined) patients, therefore the results pertain only those patients who survived after cancer diagnosis. It is quite probable that people who did not survive had more severe conditions, a shorter life expectancy and (obviously) could have been treated less intensively as regards their diabetes and diabetic complications. This should be acknowledged in the limitations of the study.

Answer: Thank you very much for your comment. It is correct that the group of patients diagnosed with diabetes who had cancer recorded before their diabetes diagnosis does not include patients with very aggressive cancers. These patients did not survive long enough to get a diabetes diagnosis. However, the group of patients with diabetes who got a cancer diagnosis after a diabetes diagnosis does indeed include all incident cancers in this patient group – inclusive more aggressive cancers.

As you comment, it is therefore quite probable that people who did not survive had more severe conditions, and could have been treated less intensively as regards their diabetes and diabetic complications. We have therefore acknowledged this consideration in the limitations of the study on P 12 L291-298:

“The group of patients who had cancer recorded before the diabetes diagnosis included only patients who had survived this cancer, and it did not include patients with terminal cancers as this was an explicit exclusion criterion. The group of patients who got a cancer diagnosis after the diabetes diagnosis did include more aggressive type of cancers. It is, therefore, a limitation of the present study that the effect of cancer was modeled without taking the timing of the cancer diagnosis into account. People who did not survive, probably had more severe conditions and could have been treated less intensively as regards their diabetes and diabetic complications”.

2. **Abstract (Results):** "The intervention reduced the risk of both these endpoints in patients without cancer. However, there was no statistically significant difference in the effectiveness of the intervention among patients with and without cancer." Perhaps better: "[...]. Furthermore, there was no statistically significant difference…"

Answer: We have rewritten the sentence on Page 2 Line 43-45 according to your suggestion.

“Furthermore, there was no statistically significant difference in the effectiveness of the intervention among patients with and without cancer.”

3. **Page 3:*** "The coexistence of cancer and diabetes may hamper the management of type 2 diabetes". Personally I do not think that a cancer diagnosis may hamper the management of T2D. Rather, I think that diabetes management (goals setting, therapy, blood glucose monitoring intensity, etc.) should take into account important comorbidities (such as cancer) as well as life expectancy, having in mind that the goal of diabetes management in many of these patients is to guarantee better nutritional status and quality of life (instead of preventing long-term diabetes complications. I think that the Authors might find of help the following references:


Answer: Thank you very much for your suggestions regarding references. We have rewritten the paragraph on P. 3 line 65-72 and included some of the suggested references.

“Treating patients with both cancer and diabetes to diminish symptoms and improve quality of life is important. However, the management of diabetes in cancer patients is often complicated [6, 7]. For instance, the diagnosis and treatment of cancer may distract both patients and health care providers from the appropriate management of diabetes. E.g. older studies show that regular chronic care of, e.g. DM, COPD, and CVD is less common in patients who have completed primary cancer treatment compared to patients with no cancer [8-11], implying that for cancer
patients with diabetes, both mortality and incidence of complications are increased compared to cancer patients without diabetes [12, 13]."

4. Discussion, Page 11: "[…] difficulties meeting treatment goals for HbA1c and LDL-cholesterol". Perhaps blood pressure targets should be added, too.

Answer: Yes, you are right in that comment, e.g., Calip et al. found decreased adherence to antihypertensive treatment. We have added this on Page 11 line 264-267.

Further, management of chronic diseases in patients with cancer is connected with lower testing rates [10] and lower adherence to medication [30, 31] resulting in difficulties meeting treatment goals for HbA1c, LDL-cholesterol and blood pressure targets [32].

5. There are a few typos and errors in the text that should be corrected

Answer: Thank you. We have now proofread the document again.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

Statistics - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study
INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: Overall, this was a well done study and an interesting addition to the literature on diabetes and cancer. I have some specific comments/queries, listed below:

1. Why was follow-up censored at 2008?

Answer: Thank you for your comment. We chose to censor follow-up 2008, as we had enough outcomes at that time. However, we are planning to do a 30-years follow-up in 2020-2021.

2. Should the authors consider further adjustment of cox models for insulin given its known association with cancer?

Answer: Thank you for your comment. Since the patients at baseline are newly-diagnosed with diabetes, they are not treated with insulin yet. However, during the 6-year follow-up, we observed that the treatment was intensified with insulin for a small fraction of patients. As you suggest, we have now added anti-diabetic treatment at the time of follow-up in both table 1 and Table 1b. Since the purpose of initiating insulin treatment probably was to prevent long-term diabetes complications in the patients, we have not adjusted for insulin as regards the association with cancer. Considering this research question, whether insulin treatment would have an impact on cancer outcome, was not a part of the study.

3. Table 1, I would consider adding the group of diabetes and noncancer in this table for comparison.

Answer: Thank you for your comment. We have now included a Table 1b, which shows diabetes patients without cancer at diagnosis and after follow-up.

4. Figure 2 is missing legend defining what the two lines represent.

Answer: Thank you for your comment. We have now added a legend to Figure 2
5. I would steer away from stating that this study is population-based or representative of type 2 diabetes patients. By virtue of this being a RCT, and patients chosen from select GP settings, it cannot be population-based.

Answer: Thank you for your comment. We have now steered away from stating that the study is representative according to your comment.