Author’s response to reviews

Title: The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data

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Author’s response to reviews:

Manuscript “The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data” by J. Czwikla, K. Jobski and T. Schink (BMRM-D-17-00141)

Dear Prof. Haneuse,

Thank you for giving us the opportunity to submit a revised manuscript. We also thank you and Mr. Goldsbury very much for your valuable time and your constructive comments which were very helpful to improve the manuscript. We performed several additional analyses and revised the manuscript according to your suggestions and feel that we were able to fully address the raised points.

Our study wants to make both researchers and readers aware that the identification of incident cancer cases in administrative data is not straightforward. It shows how different choices of the lookback period and the definition of confirmatory events impact the number of cancer cases classified as incident. We believe that this is important as our results show that the choice of these parameters has a large effect on study results. Researchers need to be aware of the consequences of their choices to be able to look for the best algorithm depending on their research question. We also believe that our results are important for all readers as they need to be aware of the mechanisms of misclassification in the identification of incident cancer cases in administrative data so that they can assess the potential bias. And finally, our results suggest that studies examining the accuracy of cancer diagnoses based on administrative data should consider several choices of the lookback period and the definition of confirmatory events to show how these parameters impact the validity.
The revised version of the manuscript and our point-by-point response were reviewed and approved by all authors.

All authors declare that they have no conflict of interest.

Informed consent was not required by law, since the study was based on pseudonymous data.

Yours sincerely, on behalf of all authors,

Jonas Czwikla, M.A.

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Editor Comments:

Overall I found this paper to be very well written. My primary concern, however, is the limited scope of what readers will be able to take away from it. The results are not really surprising (i.e. that there is an impact of lookback period) and, while the quantification of the impact on the estimates of incidence is interesting, it does not provide much guidance on what readers will really want to know which is how accurate an administrative data-based diagnosis of cancer is. For that, as the authors acknowledge in the Discussion, the administrative data would need to be linked to the registry data so that measures such as sensitivity and specificity could be investigated. That this is not possible, unfortunately, limits the contribution. Coupled with this is that the authors don’t really provide any guidance in the Discussion about what researchers can take away from this other than the optimal algorithm depends on the specifics of their research questions and context. This is, no doubt, true but it also doesn’t provide any practical guidance on how to make decisions. While I realize that linkage with registry data is likely not feasible in order for the paper to be publishable greater emphasis needs to be placed on what readers can get from the paper, as well as how future research might shed further light on these issues.

Authors’ response: We agree that the accuracy of cancer diagnoses based on administrative data is an important question. However, this was not the aim of our study in which we aimed to make both researchers and readers aware that the identification of incident cancer cases in administrative data is not straightforward and show how different choices of the lookback period and the definition of confirmatory events impact the number of cancer cases classified as incident. As our results demonstrate that the choice of these parameters has a large effect on study results, we conclude that this is an important issue that needs to be considered when using administrative data for research purposes. Researchers need to be aware of the consequences of their choices and thus look for the best algorithm depending on their research question.
Furthermore, we recommend performing sensitivity analyses to examine the robustness of the results and encourage researchers to clearly describe how incident cancer cases were identified. We also believe that our results are important for all readers as they need to be aware of the mechanisms of misclassification in the identification of incident cancer cases in administrative data so that they are able to assess the potential bias. Finally, our results indicate that studies examining the accuracy of cancer diagnoses based on administrative data should consider several choices of the lookback period and the definition of confirmatory events to show how these parameters impact the validity.

Following your suggestion to greater emphasize what readers can get from the paper, we rephrased our conclusion in the abstract as follows (page 2, lines 44-49):

“The choice of lookback and confirmation periods and the definition of confirmatory events have considerable impact on the number of incident cancer cases identified and ACI estimated. Researchers need to be aware of potential misclassification when identifying incident cancer cases in administrative data. Further validation studies should consider several choices of lookback and confirmation periods and the definition of confirmatory events to show how these parameters impact the validity.”

We further modified the “Conclusions” section as follows (page 15, lines 362-373):

“The choice of the length of the lookback period, the length of the confirmation period and the definition of confirmatory events have a considerable impact on the number of incident cancer cases identified and ACI estimated. It is not possible to give general recommendations, as the optimal algorithm depends on the characteristics of the specific cancer site, the characteristics of the available data and the underlying research question. However, we discourage from using lookback periods of 1 year and recommend using lookback periods of 2 or more years. Moreover, we recommend confirming incident cancer diagnoses using confirmation periods of at least 1 quarter. In the light of our findings, we advise to carefully consider which algorithm to use, to clearly describe how incident cases were identified and to perform sensitivity analyses to examine the robustness of the results. Further validation studies should consider several choices of lookback and confirmation periods and the definition of confirmatory events to show how these parameters impact the validity.”

Moreover, we added the following sentences to the “Discussion” section:

Page 11, lines 275-276: “We therefore suggest applying longer confirmation periods for less aggressive cancers, but more strict criteria for aggressive cancers.”

Page 11, lines 280-282: “Therefore, we suggest considering death as a potential confirmatory event when identifying incident cases for cancer sites which have a higher lethality.”
We thus recommend confirming incident cancer diagnoses using confirmation periods of at least 1 quarter. Both the exact length of the confirmation period and the definition of confirmatory events should be defined according to the characteristics of the specific cancer site, taking account of the available data and the underlying research question.

Specific comments:

Page 4, line 84: Explain left-censoring for the general readership.

Authors’ response: Thank you for this comment. We rephrased the sentence as follows (page 5, lines 109-110):

“However, the longer the lookback period the greater the number of cases that cannot meet the requirement as not enough observation time before the case is available in the database.”

Page 5, line 110: How many people were excluded because of these restrictions? Do you think that these individuals are different in some way that could lead to selection bias of the results presented?

Authors’ response: Thank you for this comment. Among 6,813,673 insured persons with at least 7 years of continuous insurance on 01 January 2013, a total of 50,124 insured persons (0.7%) were excluded since they (1) had missing or invalid information on sex (n = 18), (2) had missing or invalid information on year of birth (n = 472), (3) had missing or invalid information on place of residence (n = 30,750) or (4) resided outside of Germany (n = 18,884). Altogether, these exclusions led to a study population of 6,763,549 insured persons with at least 7 years of continuous insurance.

As the numbers of exclusions due to missing or invalid information on sex and year of birth are very small, no selection bias is introduced. The exclusions regarding the place of residence are necessary as patients living outside of Germany are (1) not captured in the German cancer registries and thus not included in our benchmark data and (2) might receive care outside the German Statutory Health Insurance.

To address these issues, we revised the “Study design and population” section and the “Results” section as follows:

“Study design and population” section (page 6, lines 136-142):
“The study population comprised all insured persons with at least 7 years (or at least 1 year in a sensitivity analysis) of continuous insurance (i.e. no insurance gaps of more than 28 days) on 01 January 2013. Insured persons with missing or invalid information on sex, year of birth or place of residence were excluded. Insured persons who resided outside of Germany were also excluded as they (1) are not captured by the German cancer registries and thus not included in our benchmark data and (2) might receive care outside the German SHI.”

“Results” section (page 8, lines 194-200):

“31,240 insured persons with at least 7 years of continuous insurance were not included in the study population because of missing or invalid information on sex (n = 18), year of birth (n = 472) or place of residence (n=30,750). Further 18,884 insured persons were not included since they resided outside of Germany. Insured persons with missing or invalid information on place of residence or places of residence outside of Germany were with an average age of 47.5 years slightly younger than the study population with 51.9 years.”

Page 5, line 129: It isn’t clear what this sentence means.

Authors’ response: We revised the sentence as follows (page 7, lines 160-161):

“Insured persons with two incident cancers (breast and colorectal for women; prostate and colorectal for men) in 2013 were counted in each entity.”

Page 6, line 145: Does ZfKD use the same operational definitions as the authors used in the administrative data? For example, are the age-standardized rates from ZfKD based on the same 1976 population?

Authors’ response: We used the same operational definitions as the ZfKD. More specifically, we used the same ICD-10 codes as the ZfKD to identify incident breast, prostate and colorectal cancer cases (page 6, lines 144-148). We also used the same methods to estimate crude and age-standardized cumulative incidences. Therefore, age-standardized cumulative incidence estimates in both administrative data and registry data are based on the same 1976 European Standard Population. For clarification, we rephrased the following sentence in the “Statistical Analyses” section (page 7, lines 176-178):

“In accordance with the ZfKD, crude cumulative incidences (CCI) and age-standardized cumulative incidences (ACI) were estimated, the latter by using the same 1976 European Standard Population”
Page 7, line 163: Can you provide the reasons why the 486 patients no longer contributed to the numerator? Similarly for all other such numbers?

Authors’ response: The 486 insured persons contributed no longer to the numerator since they were identified as prevalent or recurrent when using a lookback period of 2 years instead of only 1 year. This applies also for all other such numbers. To clarify this point, we revised the section as follows (pages 8-9, lines 202-206):

“By extending the lookback period to 2 years, the number of incident cancer cases declined by 486 (-4.7%), 284 (-4.6%) and 341 (-5.2%), respectively, since these cases had a respective cancer diagnosis in the second year of lookback period and, therefore, were classified as prevalent or recurrent.”

Page 8, line 194: It is not clear what the reader is supposed to get from this very brief mention of the regional estimates.

Authors’ response: Thank you for this comment. Results from the ZfKD and the Association of Population-based Cancer Registries in Germany (GEKID) indicate that the incidence of cancer diseases differs between the federal states (Länder) of Germany (see Table 2 columns 3, 6, 9 and 12). Therefore, we decided to calculate regional incidence estimates by using claims data of the BARMER Statutory Health Insurance fund and to examine the comparability of regional incidence estimates between both data sources. Interestingly, we found similar trends when comparing both data sources.

For clarification, we modified the following sentence in the “Statistical analysis” section (pages 7-8, lines 178-182):

“As results from the ZfKD and the Association of Population-based Cancer Registries in Germany (GEKID) indicate that the incidence of cancer diseases differs between the 16 federal states (Länder) of Germany, ACI were stratified by state to compare regional ACI estimates to regional GEKID data [18].”

Moreover, we rephrased the following sentence in the “Results” section (page 10, lines 242-243):

“Our regional ACI estimates for breast, prostate and colorectal cancer indicated similar regional variations when compared to GEKID data (Table 2).”
Page 8, line 206: Similar to my comment above, can the reasons for the false positives be ascertained? If not, the authors should at least speculate.

Authors’ response: Thank you for this comment. We believe that three principal reasons are responsible for the observed declining number of incident cancer cases when using a lookback period of 2 or more years instead of only 1 year: First, a proportion of prevalent cancer cases might not have had a respective cancer diagnosis in a lookback period of only 1 year since they decided to forego treatment options financed by the German Statutory Health Insurance. Second, recurrent cancer cases might not have had a respective cancer diagnosis during a lookback period of 1 year since the period between onset and recurrence of the disease was longer than 1 year. Third, prevalent cancer cases might not have had a respective cancer diagnosis in a lookback period of only 1 year since they were treated by active surveillance or watchful waiting. This might be particularly the case for less aggressive tumors such as prostate cancer. We addressed these aspects by adding the following passage to the “Discussion” section (pages 10-11, lines 253-260):

“The number of identified incident breast, prostate and colorectal cancer cases declined substantially with a lookback period of 2 or more years instead of only 1 year, indicating a large number of false positives when using the shortest lookback period. We believe that the principal reasons for the declining number of incident cancer cases are (1) prevalent cancer cases that decided to forego treatment options financed by the SHI, (2) recurrent cancer cases with a period between onset and recurrence of the disease longer than the respective lookback period and (3) prevalent cancer cases that are treated by active surveillance or watchful waiting (particularly in the case of prostate cancer).”

Reviewer reports:

David Goldsbury (Reviewer 1): Thank you for the opportunity to review this article. This is a useful paper about methods for identifying incident cancer cases in administrative data that will support further research using these data. It is a good additional use of information that is already routinely collected and the authors have tested many scenarios for the best use of these data. The paper is an important resource for highlighting that caution is required in using these data to estimate cancer incidence. The manuscript is of good quality and is clear and well written. There are some minor corrections and/or suggestions but overall the authors are to be congratulated for the quality of the paper.

What are the results for an algorithm without a confirmation record? It is very plausible that someone might only have one record and therefore not have the chance to have a confirmation record. Given the difference in results for confirmation periods of 1 quarter and 4 quarters, this would form another useful component of sensitivity analyses.
Authors’ response: Thank you for this comment. Preliminary analyses showed that ACI estimates are much higher when no confirmatory event is required, suggesting a relatively high number of “false positives”. Additionally, in Germany, outpatient diagnoses need to fulfill the so-called “M2Q-Criterion” (diagnoses in two different quarters) to be considered for the morbidity-oriented risk structure compensation scheme (Morbi-RSA) which aims to balance the morbidity burden between the currently 113 Statutory Health Insurance funds. Since cancer diagnoses have relevance for the Morbi-RSA, it can be assumed that incident cancer cases get at least two diagnostic records within a certain period.

However, following your suggestion, we added two algorithms where no confirmatory event is required in a lookback period of 1 and 7 years, respectively. We changed the “Methods” section accordingly (page 7, lines 163-174). The results are described on pages 9-10 (lines 214-216, lines 223-224, lines 230-231 and lines 239-241) and discussed on page 12 (lines 291-293 and lines 305-307). Furthermore, we revised Table 1, Figure 1, Table A.1, Table A.2, Figure A.1 and Figure A.2.

Indicate earlier in the paper that it is a form of ecological study, as there is no actual linkage between cancer registry and the other administrative data for validation. This wasn't clear until towards the end of the paper (line 284).

Authors’ response: Thank you for this comment. We now emphasize this issue earlier in the paper by revising the last sentence in the “Background” section as follows (page 5, lines 113-117):

“As, to our knowledge, this has yet not been systematically studied, the aim of this study was to examine the impact of (1) the length of the lookback period, (2) the length of the confirmation period and (3) the definition of confirmatory events on both the number of incident cancer cases identified and cumulative incidences estimated in administrative claims data using German cancer registry data as a benchmark at the population level.”

Indicate in the abstract that the data relate to Germany. e.g. line 32 "using German cancer registry data as a benchmark".

Authors’ response: Thank you for this comment. As suggested we rephrased the first sentence in the abstract as follows (page 2, lines 29-32):

“This cohort study examined the impact of the lengths of lookback and confirmation periods as well as the definition of confirmatory events on the number of incident cancer cases identified and age-standardized cumulative incidences (ACI) estimated in administrative data using German cancer registry data as a benchmark.”
Furthermore, we rephrased the last sentence in the “Background” section as follows (page 5, lines 113-117):

“As, to our knowledge, this has yet not been systematically studied, the aim of this study was to examine the impact of (1) the length of the lookback period, (2) the length of the confirmation period and (3) the definition of confirmatory events on both the number of incident cancer cases identified and cumulative incidences estimated in administrative claims data using German cancer registry data as a benchmark at the population level.”

Please explain the meaning of "status post" (lines 102, 121).

Authors’ response: We added the following explanation of “status post” (pages 5-6, lines 128-131):

“Since 2004, in Germany, additional coding of diagnostic certainty, which differentiates between G (certain), V (suspected), Z (status post, i.e. (asymptomatic) status after a previous diagnosis) and A (diagnosis excluded) is mandatory for outpatient diagnoses.”

The relevance of the exact outpatient diagnosis dates mentioned in line 105. It wasn't clear if these were actually used. What were the proportions of diagnosis dates assigned using exact dates and quarterly dates? This could impact upon the temporality of estimates.

Authors’ response: Thank you for this comment. In Statutory Health Insurance claims data, exact dates are available for inpatient diagnoses as well as for data on health care provision (EBM and OPS codes). Outpatient diagnoses can only be assigned quarterly. Since we decided to consider both inpatient and outpatient diagnoses in our analyses, we identified all incident cancer cases uniformly on a quarterly basis. To clarify this, we now write in the “Case definition” section (page 6, lines 148-150):

“Incident cancer cases were identified on a quarterly basis considering outpatient diagnoses coded as “certain” and hospital discharge diagnosis reflecting the reason for hospitalization.”

In the limitations (lines 293-295) the authors seem to be suggesting that the benchmark cancer registry data are not valid. I suggest re-phrasing this to say the cancer registry data are not perfect but still provide a valid benchmark, if that is the case.
Authors’ response: Thank you for this suggestion. We did not want to imply that the cancer registry data are not valid, but say that these data are only estimates and thus have some limitations, too. Therefore, we rephrased the last sentence in the “Strength and Limitations” section as follows (page 14, lines 355-358):

“However, the ACI presented by the ZfKD are estimates based on the numbers or expected values of the regional cancer registries and thus have some limitations, too. Despite these methodological issues regarding completeness of data, the ZfKD estimates still provide a valid benchmark.”

The keywords (line 49) include "pancreatic neoplasms", this should be "prostate neoplasms".

Authors’ response: Thank you for this comment. We replaced the keyword “Pancreatic Neoplasms” by “Prostatic Neoplasms” and reordered the keywords as follows (page 3, lines 50-52):

“Neoplasms · Breast Neoplasms · Prostatic Neoplasms · Colorectal Neoplasms · Incidence · Administrative Claims · Validation · International Classification of Diseases · Epidemiology · Health Services Research”

Grammatical issue line 225 "twice as much the number of".

Authors’ response: Thank you for this comment. We rephrased this text passage as follows (page 11, lines 277-280):

“Concerning the definition of confirmatory events, the exclusion of death as a confirmatory event slightly reduced the number of incident breast and prostate cancer cases which have a lower lethality. For incident colorectal cancer cases, which have a higher lethality, the observed reduction was more than twice as high.”

Grammatical issue line 233 "or is treated non-operative palliative or curative (colorectal).”

Authors’ response: Thank you for this comment. We rephrased the sentence as follows (pages 12, lines 286-290):

“Reportedly, depending on the characteristics of the patient and the tumor, a non-negligible proportion of primary cancer cases does not receive surgical treatment (breast), is treated by
active surveillance or watchful waiting (prostate) or is treated non-operatively by palliative or curative care (colorectal) [22-24].”

If looking to tighten up the tables, the denominators in Tables 1, A1 and A2 could be listed in a footnote rather than taking up 3 separate columns or repeated values.

Authors’ response: Thank you for this suggestion. In Tables 1 and A.1, we added the denominators to the header and deleted the columns with the identical numbers. In Table A.2, however, we did not change the table as the denominators differ for each choice of lookback period.

The word "respective" is used in several places where it isn't needed (e.g. lines 124, 212). This might just be a stylistic issue and if everyone else is OK with these then I am comfortable with it.

Authors’ response: Thank you for this recommendation. We deleted the word “respective” in cases where it is not needed (page 4, lines 95-97; page 10, lines 238-239) and rephrased some passages (pages 6-7, lines 154-159; page 7, lines 160-161; page 11, lines 272-275; page 12, lines 294-297). However, in some cases, we think the word “respective” is necessary to clarify that in the lookback period and the confirmation period the assessment was not based on all (three) cancer sites together but specific for each cancer site.