PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A retrospective cohort study of androgen deprivation therapy and the risk of diabetes in men with prostate cancer in Lithuania
AUTHORS	Drevinskaite, Mingaile; Patasius, Ausvydas; Kincius, Marius; Urbonas, Vincas; Smailyte, Giedre

VERSION 1 – REVIEW

REVIEWER	Richards, Kyle The University of Chicago Medical Center
REVIEW RETURNED	24-Nov-2020

GENERAL COMMENTS	The authors performed a retrospective analysis to examine the risk of DM developing in prostate cancer patients receiving ADT. Methods: 1. The authors state: “In order to evaluate incidence of diabetes caused by ADT…” Can you say that the ADT caused the DM in this retrospective study? 2. How did you define ADT use? This was not clear in the methods. Was this any ADT use? Was a specific duration of ADT use required? You state: “Association between duration of GnRH agonists use and diabetes risk was assessed by dividing duration into the following intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years” but this requires additional explanation. 3. Was duration of ADT use cumulative duration? Results: 1. Table 1: It looks like there were significant differences in baseline characteristics between the ADT free and ADT cohort. This requires p value and commentary. 2. Table 3: from the table, it is not clear what variables were put in your model. There is an asterisk in the table but no explanation of what this means. 3. Table 4: 0-1 year of exposure makes no sense. Did you really include people that had no exposure to ADT in this cohort? Or should this be < 1 year of exposure? 4. Table 4: what is your referent group?

REVIEWER	Du, Xianglin The University of Texas Health Science Center at Houston School of Public Health, Department of Epidemiology, Human Genetics and Environmental Sciences
REVIEW RETURNED	28-Dec-2020

GENERAL COMMENTS	This study aimed to use the Lithuanian Cancer registry and National Health Insurance Fund (NHIF) linked database to

	examine the risk of type 2 diabetes in prostate cancer patients and its association with androgen deprivation therapy. Because many studies on this topic have been published, it is unclear what this study adds to the existing literature. Also, there are a number of concerns. If these comments/concerns can be addressed well, the quality of the reporting should be substantially improved. 1). Because there already were several studies that demonstrated the association between ADT and the risk of diabetes, this manuscript should describe what this study added to the existing literature. 2). Make it clearer the study design as a retrospective cohort study. Also make it clearer how the study outcome on diabetes was identified from the registry/National Insurance Data. If it was through the diagnosis and/or procedure codes, list them all. 3). Major concern was the section bias for main exposure groups (ADT users vs. non-ADT groups). As author also indicated, those ADT users might have severe or advanced metastatic prostate cancer. Hence, ADT use might be a major confounding by indication. By adjusting for stage alone may not be sufficient. One way to help minimize this bias is to perform a propensity score-adjusted or matched analyses. More clinical or socio-democratic information such as Gleason score or cancer grade etc. should be included as many as possible. 4). Table 1 compared ADT vs no-ADT groups. They should put the AA and GnRH under the ADT users to avoid confusion. Also, show statistical differences between comparison groups. 5). Table 2 showed the incidence rates by number of cases per person years, but no person years were shown in each categories of ADT treatment groups. They should have presented this information in the table and also show the cumulative incident rates in the table as well as in the text. 6). Table 3 had aHR*, but did not indicate what the regression model adjusted for. Provide this information in the footnote of this Table as well as in Table 4. 7). Surprisingly as they showed that there was no relationship between the risk of diabetes and the longer duration of ADT uses if the ADT was associated with the increased risk of diabetes. Perhaps, this study was affected by the selection bias that was mentioned in above point #3. The study should show how many doses were received per month or per year in association with the outcomes. 8). Many key grammatical errors: such as ‘adrogen’ and ‘strengthts’ in Abstract page. Correct them.

REVIEWER	Adolfsson, Jan Karolinska Institute
REVIEW RETURNED	29-Dec-2020

GENERAL COMMENTS	This paper investigates the risk of diabetes mellitus type 2 (T2DM) in men with prostate cancer and on androgen deprivation therapy (ADT). This was investigated in a national sample in Lithuania.

	The risk was increased in those on GnRH-agonists but not in men on androgen compared with men with prostate cancer but with no ADT. As pointed out by the authors, much of this is already known but can also be seen as corroborating previous published findings. The manuscript is well written and succinct. It would be of interest to know the validity, e.g. the coverage, of the cancer registry. The analysis seems to be adjusted for tumour stage only, I presume that the authors also have access to age which in the that case should be adjusted for. Still the difference between GnRH and antiandrogens could be due to residual confounding. Percentages are given with two decimals all trough the manuscript and in the tables. This should at least be rounded to one decimal. Two decimals give a false impression of precision.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kyle Richards, The University of Chicago Medical Center

Methods:
1. The authors state: “In order to evaluate incidence of diabetes caused by ADT…” Can you say that the ADT caused the DM in this retrospective study?
Sentence has been changed to “In order to evaluate the risk of developing diabetes among ADT users in prostate cancer patients’…..“.

2. How did you define ADT use? This was not clear in the methods. Was this any ADT use? Was a specific duration of ADT use required? You state: “Association between duration of GnRH agonists use and diabetes risk was assessed by dividing duration into the following intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years” but this requires additional explanation.
As ADT users were defined men who received GnRH agonists or antiandrogens for at least 6 months. GnRH agonists users to the duration group were assigned by cumulative exposure.
Now it is clarified in the methods section.

3. Was duration of ADT use cumulative duration?
Covered by the answer to the previous comment. Now it is clarified in the methods section.

Results:
1. Table 1: It looks like there were significant differences in baseline characteristics between the ADT free and ADT cohort. This requires p value and commentary.
According to the reviewer proposal we added p values to the Table 1 and one sentence in the Results section.

2. Table 3: from the table, it is not clear what variables were put in your model. There is an asterisk in the table but no explanation of what this means.
Age and stage were put into the model The explanation has been added to the Tables 3 and 4.

3. Table 4: 0-1 year of exposure makes no sense. Did you really include people that had no exposure to ADT in this cohort? Or should this be < 1 year of exposure?
0-1 it has been changed into <1 year of exposure in the Table 4.

4. Table 4: what is your referent group?
Our referent group was ADT free cohort; now it is added to the Table 4.

Reviewer: 2
Dr. Xianglin Du, The University of Texas Health Science Center at Houston School of Public Health

1). Because there already were several studies that demonstrated the association between ADT and the risk of diabetes, this manuscript should describe what this study added to the existing literature.

We agree that our study results lack scientific novelty, however association is consistent when results are replicated in studies in different settings using different methods (Hill's criteria of causation, Porta, 2018) and in some situation replications would have positive value and would help to prove results of original discovery research (Ioannidis JPA. Why replication has more scientific value than original discovery. Behav Brain Sci. 2018). Therefore, we strongly believe that our study will contribute to existing evidence regarding the risk of diabetes in prostate cancer patient cohort.

2). Make it clearer the study design as a retrospective cohort study. Also make it clearer how the study outcome on diabetes was identified from the registry/National Insurance Data. If it was through the diagnosis and/or procedure codes, list them all.'

We corrected Methods section in order to meet reviewer comments.

3). Major concern was the section bias for main exposure groups (ADT users vs. non-ADT groups). As author also indicated, those ADT users might have severe or advanced metastatic prostate cancer. Hence, ADT use might be a major confounding by indication. By adjusting for stage alone may not be sufficient. One way to help minimize this bias is to perform a propensity score-adjusted or matched analyses. More clinical or socio-democratic information such as Gleason score or cancer grade etc. should be included as many as possible.

We completely agree with reviewer comment on possible biases due to different stage distribution between ADT users and non-users. Proposed by the reviewer propensity score matching is usually used when study is dealing with large number of covariates. Unfortunately, no information on socioeconomic status and other important clinical characteristics were available from Cancer Registry and NHIF database. The only documented clinical variable in our study was stage of disease, therefore we feel that additional analysis will not add any new information to the study results.

4). Table 1 compared ADT vs no-ADT groups. They should put the AA and GnRH under the ADT users to avoid confusion. Also, show statistical differences between comparison groups.

We have changed the design of Table 1 and added p values to show differences between comparison groups.

5). Table 2 showed the incidence rates by number of cases per person years, but no person years were shown in each categories of ADT treatment groups. They should have presented this information in the table and also show the cumulative incident rates in the table as well as in the text.

We have added person-years to the Table 2 as proposed by reviewer.

6). Table 3 had aHR*, but did not indicate what the regression model adjusted for. Provide this information in the footnote of this Table as well as in Table 4.

We have added the explanation of the asterix.

7). Surprisingly as they showed that there was no relationship between the risk of diabetes and the longer duration of ADT uses if the ADT was associated with the increased risk of diabetes. Perhaps, this study was affected by the selection bias that was mentioned in above point #3. The study should show how many doses were received per month or per year in association with the outcomes.

This answer partly covered by answer to the Reviewer's 1 question no.3. Duration of ADT therapy in this analysis was used as an indicator of cumulative exposure or dose, as patients who received ADT were under continuous androgen deprivation.

8). Many key grammatical errors: such as ‘adrogen’ and ‘strengthts’ in Abstract page. Correct them.

We have corrected typo errors.

Reviewer: 3
Dr. Jan Adolfsson, Karolinska Institute

1. It would be of interest to know the validity, e.g. the coverage, of the cancer registry.

Since the period 1988–1992, the Registry data have been included in the ‘Cancer Incidence in Five Continents’ and the quality of the Registry data meets international standards; the death certificated only (DCO) cases account 1.5% all registered BC cases, 92.5% of them are morphologically verified [Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J, editors (2013). Cancer Incidence in Five Continents, Vol. X (electronic version). Lyon: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr,].

2. The analysis seems to be adjusted for tumour stage only, I presume that the authors also have access to age which in the that case should be adjusted for. Still the difference between GnRH and antiandrogens could be due to residual confounding.

The analysis is adjusted to stage and age.
We agree, that difference between GnRH and antiandrogens could be due to residual confounding. This limitation is mentioned in Discussion part.

3. Percentages are given with two decimals all trough the manuscript and in the tables. This should at least be rounded to one decimal. Two decimals give a false impression of precision.

We have changed decimals from two to one in percentages.

VERSION 2 – REVIEW

REVIEWER	Richards, Kyle The University of Chicago Medical Center
REVIEW RETURNED	21-Mar-2021

GENERAL COMMENTS	The authors have now addressed my comments adequately.

REVIEWER	Adolfsson, Jan Karolinska Institute
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	Better this time. No specific comments this time. Could perhaps benefit from a linguistic review Again, much of this is already known and the news value can be seen as limited. However, the analysis over treatment time is of interest (corroborates previous data, ref 12 in the ms).

REVIEWER	Du, Xianglin The University of Texas Health Science Center at Houston School of Public Health, Department of Epidemiology, Human Genetics and Environmental Sciences
REVIEW RETURNED	06-Apr-2021

GENERAL COMMENTS	no more comments.