

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

Title (Provisional)

Cancer prevalence after exposure to Wnt-activating drugs: a systematic review

Authors

aLKASHAF, AhmeD; Smith-Cortinez, Natalia; Fenton , Georgina; Bok, Sebastian Thomas; Stokroos, Robert; Stegeman, Inge; Straatman, Louise V.

VERSION 1 - REVIEW

Reviewer	1
Name	Puglisi, Fabio
Affiliation	University of Udine
Date	04-Oct-2024
COI	None

The manuscript addresses an important topic, focusing on the implications of Wnt pathway activation through drug exposure and its association with cancer prevalence. This is a timely and pertinent topic given the ongoing research into Wnt pathway modulators in cancer and regenerative medicine.

Minor points

- the abstract could benefit from a slight restructuring to present the main findings more prominently. The impact of the findings on the field could be highlighted more clearly in the conclusions section
- Bias was minimized through independent screening by two authors, but details on the resolution of discrepancies during data extraction is suggested
- the discussion could be strengthened by more critically addressing potential limitations of the studies included in the review, such as variations in study design and the quality of the included studies

Reviewer	2
Name	Nguyen, Huyen
Affiliation	College of Health Sciences
Date	04-Oct-2024
COI	None

The protocol was registered in 2021 and its research question is not fully matched with the one in manuscript; I would suggest to revise research question and adding meta analysis for this manuscript.

Some specific comments are below:

Search strategy: Why the team only focused on on 3 databases: PubMed, Embase and Cochrane databases? Will it lead to limitation of the searched and included studies?

Data extraction – line 51-52 page 6 "Authors were contacted if data was not reported in the article or otherwise unavailable" – Was there any case that you could not contact and then no data for reporting? How many studies were excluded due to this reason?

Critical Appraisal: - line5-6 page 7 "The methodological quality of included articles was assessed using the Newcastle Ottawa-Scale (NOS) for nonrandomized studies as a reference guide" ♦ Can you link to the reference guide?

Statistical Methods: I would suggest the team do perform meta-analysis to establish statistical significance with studies that have conflicting results. This will help to confirm the conclusions of the research.

Reviewer	3
Name	Kelson, Zoe
Affiliation	University of Exeter
Date	04-Oct-2024
COI	None

This study aims to assessing whether the use of drugs that activate the Wnt pathway leads to an increased cancer risk.

Reviewer comments:

" The search string, objectives, and study protocol methods were defined before the study was initiated" Can the authors please confirm if and where the study protocol was registered, and provide the registration number?

" This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline" Thanks for providing a copy of the PRISMA checklist.

" PubMed, EMBASE and Cochrane databases were searched. All articles until November 17th 2023 were included." Can this review please be updated prior to publication?

" Strengths and limitations of this study"

And

" Strengths and weaknesses of the review"

Can the acknowledgment of study limitations please be expanded on in these sections?

" The full search strategy can be found in Supplementary Table S1."

Can the authors please confirm in the main article if they applied any language restrictions?

" Three independent reviewers (A.A., S.B., N.S-C.) screened title and abstracts of collected studies after duplicate removal for eligibility criteria, and subsequently met and resolved disagreements. Full text screening was performed by two independent reviewers and disagreements were solved as above."

And

" A data extraction table was used to extract study characteristics and findings by two reviewers (A.A., N.S-C). with the software Microsoft Excel....

Data extraction was done by one author and checked by another author."

The authors demonstrate that they have followed rigorous article screening and data extraction processes.

" The methodological quality of included articles was assessed using the Newcastle Ottawa-Scale (NOS) for nonrandomized studies as a reference guide (GA Wells et al.n.d.). "

The authors have suitably assessed study quality. Can they please clarify how many reviewers were involved in the assessment, and how any cases of discordance were resolved?

" Results were expressed according to the reported ratios from the published studies. This includes percentages, odds ratios (OR), risk ratio's (RR) and hazard ratio's (HR), in accordance with study design and available data. When unavailable, RR's and OR's were calculated. All ratios were used to answer the main questions qualitatively. No quantitative analyses were conducted for this systematic review."

The authors clearly describe the approach taken in the Methods section.

Was an assessment of heterogeneity undertaken?

Did the authors consider undertaking a meta-analysis?

" Overall, there was

no significant increase in the cancer risk among patients exposed to drugs that have been described to activate the Wnt pathway." [Abstract]

Given the authors report a descriptive review, can they please tone down the strength of the conclusions drawn and be cautious not to infer significant (or non-significant) pooled differences (i.e. rather than 'Overall' might 'For each included study' be more accurate)?

"Risk of Bias"

Can the authors please further highlight the studies deemed to have low quality when interpreting the results and conclusions (i.e. if studies with a high risk of bias were excluded, how would the study outcomes changes)?

VERSION 1 - AUTHOR RESPONSE

In reply to reviewer #1: Dr. Fabio Puglisi University of Udine

We deeply appreciate the time and effort invested by the editors and reviewers in our manuscript. We have carefully considered all comments and suggestions and have modified the manuscript accordingly.

Reviewer commented:

Dr. Fabio Puglisi University of Udine

Comments to the Author:

The manuscript addresses an important topic, focusing on the implications of Wnt pathway activation through drug exposure and its association with cancer prevalence. This is a timely and pertinent topic given the ongoing research into Wnt pathway modulators in cancer and regenerative medicine.

Authors answer: We thank the reviewer

Minor points

- the abstract could benefit from a slight restructuring to present the main findings more prominently. The impact of the findings on the field could be highlighted more clearly in the conclusions section

Authors answer: We thank the reviewer for the suggestion. BMJ Open has clearly defined sections for the abstract so restructuring it is not a feasible option. However, we have re-written the conclusions section to highlight the main findings more prominently (lines 30-33).

Reviewer commented:

- Bias was minimized through independent screening by two authors, but details on the resolution of discrepancies during data extraction is suggested

Authors answer: We thank the reviewer. We have included the resolution of discrepancies in lines 105 and 113

Reviewer commented:

- the discussion could be strengthened by more critically addressing potential limitations of the studies included in the review, such as variations in study design and the quality of the included studies

Authors answer: We thank the reviewer for the comment. We have addressed the potential limitations of the studies in line 382

In reply to reviewer #2: Dr. Huyen Nguyen, College of Health Sciences.

We deeply appreciate the time and effort invested by the editors and reviewers in our manuscript. We have carefully considered all comments and suggestions and have modified the manuscript accordingly.

Comments to the Author:

The protocol was registered in 2021 and its research question is not fully matched with the one in manuscript; I would suggest to revise research question and adding meta analysis for this manuscript.

Authors answer: We thank the reviewer for the comment. We have addressed the suggestion regarding the research question in the manuscript (line 76 -79), which aligns with the main outcome, which is registered in the protocol in 2021: "The main outcome is the development of any type of cancer (defined below) due to the use of WNT activators"

Regarding the meta-analysis, while we considered to do a meta-analysis, regrettably the heterogeneity between the studies is too large. There is high methodological heterogeneity in the data, concerning inclusions of specific types of patients, cancer types, used medication and follow up time. With this amount of heterogeneity, it is not recommended to do a meta-analysis. <https://training.cochrane.org/handbook/current/chapter-10#section-10-10/>. Therefore, regrettably, we could not conduct a meta-analysis.

Reviewer commented:

Search strategy: Why the team only focused on 3 databases: PubMed, Embase and Cochrane databases? Will it lead to limitation of the searched and included studies?

Authors answer: We focused on these three databases because of the types of studies we searched. Medical studies will usually be covered by these databases.

Reviewer commented:

Data extraction – line 51-52 page 6 “Authors were contacted if data was not reported in the article or otherwise unavailable” – Was there any case that you could not contact and then no data for reporting? How many studies were excluded due to this reason?

Authors answer: Fortunately, we did not have to exclude any manuscripts due to this reason.

Reviewer commented:

Critical Appraisal: - line 5-6 page 7 “The methodological quality of included articles was assessed using the Newcastle Ottawa-Scale (NOS) for nonrandomized studies as a reference guide” ♦ Can you link to the reference guide?

Authors answer: The reference guide has been now cited in the text (Line 126).

Reviewer commented:

Statistical Methods: I would suggest the team do perform meta-analysis to establish statistical significance with studies that have conflicting results. This will help to confirm the conclusions of the research.

Authors answer:

We thank the reviewer for the comment. While we considered to do a meta-analysis, regrettably the heterogeneity between the studies is too large. There is high methodological heterogeneity in the data, concerning inclusions of specific types of patients, cancer types, used medication and follow up time. With this amount of heterogeneity, it is not recommended to do a meta-analysis. <https://training.cochrane.org/handbook/current/chapter-10#section-10-10/>. Therefore, regrettably, we could not conduct a meta-analysis.

In reply to reviewer #3 [statistical reviewer] Dr. Zoe Kelson, University of Exeter

We deeply appreciate the time and effort invested by the editors and reviewers in our manuscript. We have carefully considered all comments and suggestions and have modified the manuscript accordingly.

Comments to the Author:

This study aims to assessing whether the use of drugs that activate the Wnt pathway leads to an increased cancer risk.

Reviewer commented:

“ The search string, objectives, and study protocol methods were defined before the study was initiated”

Can the authors please confirm if and where the study protocol was registered, and provide the registration number?

Authors answer: Yes, the study protocol was register in PROSPERO, with registration number CRD42021286193

Reviewer commented:

" This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline"
Thanks for providing a copy of the PRISMA checklist.

Authors answer: We thank the reviewer.

Reviewer commented:

" PubMed, EMBASE and Cochrane databases were searched. All articles until November 17th 2023 were included."

Can this review please be updated prior to publication?

Authors answer: We have updated the review on November 1st 2024.

Reviewer commented:

" Strengths and limitations of this study"

And

" Strengths and weaknesses of the review"

Can the acknowledgment of study limitations please be expanded on in these sections?

Authors answer: We have expanded the study limitations, addressing the wide variety in study designs, risk of bias and heterogeneity (line 382)

Reviewer commented:

" The full search strategy can be found in Supplementary Table S1."

Can the authors please confirm in the main article if they applied any language restrictions?

Authors answer: We did not apply any language restrictions and it has been now added in Line 20 (abstract) and 93.

Reviewer commented:

" Three independent reviewers (A.A., S.B., N.S-C.) screened title and abstracts of collected studies after duplicate removal for eligibility criteria, and subsequently met and resolved disagreements. Full text screening was performed by two independent reviewers and disagreements were solved as above."

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Authors answer: We thank the reviewer.

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Ottawa-Scale (NOS) for nonrandomized studies as a reference guide (GA Wells et al.n.d.). ”
The authors have suitably assessed study quality. Can they please clarify how many reviewers were involved in the assessment, and how any cases of discordance were resolved?

Authors answer: We have added this to the text in Line 121.

Reviewer commented:

“ Results were expressed according to the reported ratios from the published studies. This includes percentages, odds ratios (OR), risk ratio’s (RR) and hazard ratio’s (HR), in accordance with study design and available data. When unavailable, RR’s and OR’s were calculated. All ratios were used to answer the main questions qualitatively. No quantitative analyses were conducted for this systematic review.”

The authors clearly describe the approach taken in the Methods section.

Authors answer: We thank the reviewer.

Reviewer commented:

Was an assessment of heterogeneity undertaken?

Did the authors consider undertaking a meta-analysis?

We thank the reviewer. While we considered to do a meta-analysis, regrettably the heterogeneity between the studies is too large. There is high methodological heterogeneity in the data, concerning inclusions of specific types of patients, cancer types, used medication and follow up time. With this amount of heterogeneity, it is not recommended to do a meta-analysis.

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Reviewer commented:

“ Overall, there was

no significant increase in the cancer risk among patients exposed to drugs that have been described to activate the Wnt pathway.” [Abstract]

Given the authors report a descriptive review, can they please tone down the strength of the conclusions drawn and be cautious not to infer significant (or non-significant) pooled differences (i.e. rather than ‘Overall’ might ‘For each included study’ be more accurate)?

Authors answer: We agree with the reviewer that we cannot make an ‘overall conclusion’ since we cannot do a meta-analyses. We have rephrased this in Lines 403-408.

Reviewer commented:

“Risk of Bias”

Can the authors please further highlight the studies deemed to have low quality when interpreting the results and conclusions (i.e. if studies with a high risk of bias were excluded, how would the study outcomes changes)?

Authors answer: We thank the reviewer. We have included in line 318, the 18 cohort studies that were assessed to have low risk of bias, showed no increased cancer prevalence.