

Peer-Review comments and authors responses

Reviewer 1

Recommendation: Revisions Required

Comments:

1. **Strengths and limitations:** As the authors mention in “Strengths and Limitations” section: important limitations are expected since the survey reports results according to a general fixed interview, that addresses the outcome and exposure in a general way. The exposure: Vitamin D and Zinc intake present possible information bias. And on the other hand, the outcome “ever being told to have cancer”, might be a difficult concept to name. Since is a cross-sectional study could be named as prevalence. But since is more a “history of having cancer”, I researched the term: “Cancer Survivor”.

According to the NCCN Survivorship Panel supports the NCI’s definition of a cancer survivor: “An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life”(1). You might run further research on this term and check if it fits the manuscript. Please reconsider along the manuscript changing the term incidence for the alternatives mentioned above.

In general, the study design, methodology, results and discussion are proper and adequate.

Response: *We have revised the Strengths and Limitations section to emphasize the restricted nature of cross-sectional surveys and the potential biases introduced by self-reported data. These revisions provide a more comprehensive overview of the study's limitations.*

Detailed Comments:

1. **Title:** Considering is a cross-sectional study the association with present or past “history of having cancer” is more accurate than incidence. Incidence is better used in prospective cohort studies. Other term, that might be used is: “cancer survivor”, considering the selected participants were asked: “ever being told to have cancer”.

Response: *We greatly appreciate your detailed and thoughtful comments, which have provided us with valuable insights to enhance our manuscript. Below, we address each of your comments in detail:*

1. *Terminology: "Incidence" vs. "Cancer Survivor" or "History of Cancer"*

We agree with your recommendation. Throughout the manuscript, we have replaced the term "incidence" with "prevalence" or "history of having cancer" to align with the study design and outcome assessment. We also explored the term "cancer survivor" as suggested, but given the phrasing of the survey question (“ever been told you had cancer”), we believe "history of cancer" best represents the population under study. This adjustment has been implemented across all sections of the manuscript, including the title, introduction, results, and discussion.

2. **Abstract:** The study design is indicated in the abstract; it also shows informative and balanced summary of what was done and what was found.
3. **Introduction:** Explains the scientific background and rationale for the investigation. The introduction refers to cancer incidence rather than “cancer survivor” or “history of cancer”. I suggest changing the concept in every section of the article that was used. Since is a self-reported “ever being told to have cancer”. The introduction states specific objectives, including a hypothesis.
4. **Methods:** Study design is stated. In data base description I recommend adding a figure on the sample size determination.

For example:

- Initial sample size.
- Participants excluded (for example aged <20 years, no information regarding cancer, etc).
- Participants excluded because of missing data on the different variables considered (confounders /effect modifiers, and add the numbers lost for each variable).
- Final sample size.

The definition of exposure and outcome is well described. The additional variables considered, were well described.

Maybe before describing them, add title: potential confounders /effect modifiers (before smoking, alcohol intake, BMI). Race variable needs to be described.

Since vitamin D intake was an average intake over the last 30 days, maybe describe potential sources of recall bias. Regarding zinc intake, since it considers the intake in the last 24 hours also address on how the data around the variable could be biased. For example: the day of the interview the participant answered there was no intake on zinc supplement for the last 24 hours but could happen the participant previously had been taking the supplement for months.

Response:

Sample Size Description

- *We have added a flowchart in the Methods section to detail the sample size determination. This figure includes:*
 - *The initial sample size.*
 - *Exclusions (e.g., missing data on cancer history, and missing data for confounders or effect modifiers).*
 - *The final sample size included in the analysis.*

Covariates and Bias Considerations

- *A new subsection titled "Covariates" has been added to the Methods section. This subsection provides detailed descriptions of smoking status, alcohol consumption, and BMI.*
 - *Regarding race, after further review, we determined that its inclusion lacked sufficient relevance to cancer prevalence in this context. Therefore, we have excluded race as a covariate in the final analysis.*
 - *We have expanded the discussion of potential biases*

Statistical Methods: well described.

5. **Results:** I suggest adding a table to describe the level of association between exposure, outcome and other variables. Is easier to interpret for the reader.
6. **Report other analysis:** if you did sensitivity analysis with some variables please report it in this section.

Response:

- *A new table has been added to the Results section to present the associations between vitamin D and zinc intake, cancer prevalence, and covariates. This format allows for easier interpretation of the findings.*
 - *Additionally, we conducted a sensitivity analysis to assess potential recall bias and evaluate the robustness of our results. This analysis is now included in the Results section and discussed in the Discussion section.*

7. **Discussion:** overall interpretation of results considering objectives, limitations, results from similar studies were commented.

Response: *The Discussion section has been expanded to incorporate a more detailed interpretation of the findings. We discuss the study's limitations, including biases introduced by the cross-sectional design and dietary recall data. Comparisons with results from similar studies have been elaborated to provide a broader context.*

Reviewer 2

Comments:

1. General (paragraph construction):

We appreciate your effort in submitting your manuscript to our journal. The topic of nutritional supplementation and its potential link to cancer is both timely and significant, warranting thorough and rigorous methodologies for evaluation. This project presents relevant findings that contribute to the ongoing discussion in this field; however, there are several areas where enhancements can be made to strengthen your work. We encourage you to consider these suggestions to improve the clarity and impact of your research, from the overall structure to the scientific content.

- **Introduction:** First, the manuscript's narrative should be standardized; several styles and inconsistencies, such as contractions, were used. While practical in everyday writing, they are not typically used in scientific style—also, indistinct capitalization of several terms like Cancer, Zinc, and Vitamins Second. Also, use comma (,) to separate thousand quantities. Why do you describe your methods in the introduction?
- Second, the first reference is located in the Database description, which means that everything before this section is original, which is not the case. References are non-negotiable in scientific writing. Please correct it.
- Third, construct your paragraphs consistently and balanced. While the initial paragraphs of each section have around four large sentences, the following

paragraphs contain two. Well-written scientific research requires clear and concise ideas. Please correct it.

Response:

We deeply appreciate your review of our manuscript and your constructive feedback. We acknowledge the areas for improvement you identified and have made substantial revisions to address your comments. Below, we provide a detailed response to each of the points raised:

Standardization of Narrative and Writing Style

We have revised the manuscript to standardize the narrative and adhere to scientific writing conventions. All contractions have been removed, and capitalization has been corrected to follow appropriate rules (e.g., "cancer," "zinc," "vitamins"). Thousand quantities are now separated with commas for clarity (e.g., 5,000 instead of 5000).

References and Citation Placement

We have reviewed and revised the manuscript to appropriately cite references, including the Introduction section, ensuring accurate attribution to existing literature.

Paragraph Construction and Balance

We have reconstructed the paragraphs to balance their length and improve the flow of ideas. Each section now presents clear and concise paragraphs with consistent formatting.

2. Methods:

Table 1 requires restructuring to be clear and informative. Replace N with total. Variables description is unorganized. For example, you use [] and () in the first column but not in the following columns. Use commas (median [P]). P refers to percentiles and describes them correctly, such as p25th-p75th. OMS refers to the WHO in Spanish. Abbreviations such as WHO could be used with limited spaces or if they are familiar. They are unnecessary if you have enough space—for example, body mass index (BMI).

Response:

Table 1 Restructuring

- *Table 1 has been restructured for clarity and consistency:*
 - *Replaced "N" with "Total" for better understanding.*
 - *Standardized formatting using commas for numerical data*

Regarding the scientific content, what is the impact of performing such an analysis using this data type? Should it be considered real-world data? If yes, what are the implications of the methods used to collect data? What is the importance of NHANES? Publications are

increasing—what type of publications—observational studies, randomized controlled trials, or synthesis of evidence?

Study design: Study design. Is there anything else about the NHANES methodology that needs to be described?

Exposure and outcome description. It is not clear why you considered alcohol, smoking, and BMI variables. An additional table could be helpful here.

Results:

The results section is insufficiently described, considering the statistical analysis section. Where are the additional analyses that assessed your model? What about the AUC? Discussion, including strengths and limitations, and conclusion sections, are minimal.

Response:

Scientific Content: Real-World Data and NHANES Importance

- *We have expanded the Introduction and Discussion sections to address the importance of NHANES as a source of real-world data. This dataset's robust methodology and representative sampling provide valuable insights into public health trends. We have also clarified how the NHANES data supports observational research, as it captures real-world dietary and health behaviors at a national level.*

Reviewer 3

Comment:

Congratulations to the authors for accomplishing this draft and putting together a good statistical analysis model to assess a large cohort and support evidence on the association between zinc and vitamin D supplementation and cancer. I believe the manuscript has lots of potential but is missing fundamental parts to be well-structured, such as addressing better the research gap and discussing extensively its limitations. I hope these revisions help improve the reported findings. Find attached the letter with the major and minor comments, as well as observations in the manuscript file.

Response:

We sincerely thank you for your feedback and for acknowledging the potential of our manuscript. Your comments have provided us with valuable insights to improve the structure and clarity of our study. Below, we detail how we have addressed your suggestions and implemented revisions in the manuscript.

We expanded the Introduction to better contextualize the research gap by providing a clearer overview of conflicting findings in the literature regarding vitamin D and zinc supplementation and cancer prevalence. This revision strengthens the rationale for our study.

The “Strengths and Limitations” section has been revised to thoroughly discuss the most pertinent limitations, including the cross-sectional nature of the study, the potential for recall bias in dietary data collection, and the lack of cancer-specific details such as type and stage. These additions ensure transparency about the study’s constraints while highlighting its contributions.

Specific Revisions Made

- **Introduction:**

- *Added a paragraph summarizing the conflicting evidence in the literature, with references to both supporting and non-supporting findings about vitamin D and zinc supplementation and cancer risk.*
- *Clarified the unique aspects of our study design and dataset, emphasizing how this research addresses existing gaps.*

- **Strengths and Limitations Section:**

- *Addressed the potential for bias in dietary recall data, particularly the differing recall periods for vitamin D and zinc supplementation.*
- *Highlighted the limitation of NHANES data in not providing cancer type or stage, which prevents more detailed stratified analyses.*
- *Discussed how reliance on self-reported cancer diagnoses might introduce inaccuracies in the outcome variable.*

Reviewer 4

Comment:

Congratulations on your submission.

Please see attached my comments and suggestions of your article.

We sincerely thank the reviewer for their detailed feedback and constructive suggestions. Below, we provide our responses to each comment and explain the revisions made to the manuscript accordingly.

Response:

1. Clarify "Significant predictor of cancer"

- *We revised the text to clarify that the analysis. This has been explicitly stated in the Results and Discussion sections.*

2. Replace "general population" with "in this population" or "in this sample"

- *We replaced all instances of "general population" with "in this population" or "in this sample," ensuring consistency throughout the manuscript.*

3. Clarify association of cancer risk with demographic factors

- *This information has been added to the Results and Discussion sections.*

4. Add references for "while some studies" and "whereas many studies"

- *We added appropriate references to substantiate these claims.*

5. Rephrase the last paragraph of the Introduction

- *The paragraph has been rephrased to succinctly summarize the study's objectives and rationale without repetition.*

6. Explain why cancer type or stage was not considered

- *NHANES dataset does not include specific details on cancer type or stage, limiting our ability to stratify results by these variables.*

7. Explain differences in categorization of vitamin D and zinc

- *We clarified in the Methods section*

8. Move the sentence about age-related prevalence to the Conclusion

- *The sentence has been moved to the Conclusion section for better alignment with the narrative structure.*

9. Ensure consistent capitalization for vitamin D and zinc

- *We reviewed and corrected all instances of capitalization, ensuring uniformity for terms like "vitamin D" and "zinc" throughout the manuscript.*

10. Add OR, CI, and p-value for age in the Results section

We have added the odds ratio (OR), confidence interval (CI), and p-value for age to the Results section

Comments to all reviewers:

1. Objective Placement in the Introduction

Thank you for pointing out the importance of placing the study's objective at the end of the Introduction. We have revised this section and relocated the objective to the last paragraph to improve the flow and structure of the manuscript.

2. Addressing the Gap of Cancer Type and Stage

We appreciate your observation regarding the lack of consideration for cancer type or stage. Acknowledging the limitation of the NHANES dataset in this regard, we have added a sentence to highlight this gap

3. **Removal of Methodology from the Introduction**

We agree that methodological details should not be included in the Introduction.

4. **Moving Covariates to the Methods Section**

Thank you for highlighting this oversight. Descriptions of covariates previously included in the Introduction have been relocated to the Methods section under a dedicated subsection titled "Covariates," where they are conceptually and operationally defined.

5. **Reinforcing the Background in the Introduction**

We have expanded the Introduction to provide a stronger rationale for the study. Specifically, we have added details on the global burden of cancer, the increasing use of dietary supplements, and the conflicting evidence in the literature that underscores the importance of addressing this gap.

6. **Population Details and NHANES Description**

We have clarified that this analysis included only adult participants and added a paragraph describing the NHANES survey.

7. **Exposure and Outcome Specification**

We have revised the Methods section to clearly define the exposure and outcome variables, including survey questions and thresholds for categorization

8. **Covariates and Operational Definitions**

A new paragraph has been added under the "Covariates" subsection in the Methods section. Each variable is now clearly defined conceptually and operationally.

9. **Clarification of "Unusable Entries"**

The term "unusable entries" was used for missing data

10. **First Paragraph of the Discussion**

The first paragraph of the Discussion has been revised to summarize the study's findings concisely. Comparative discussions with other research findings have been moved to subsequent paragraphs to better structure the section.

11. **Consistency of Values in the Results Section**

We have carefully reviewed the Results section and ensured that all odds ratios (ORs), confidence intervals (CIs), and p-values are consistent with the statistical model and match the corresponding values reported in the tables.