PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between Cancer and Contact Allergy– a linkage Study
AUTHORS	Engkilde, Kaare; Thyssen, Jacob; Menné, Torkil; Johansen, Jeanne

VERSION 1 - REVIEW

REVIEWER	***Howard Maibach*** Department of Dermatology, University of California, San Francisco, USA No competing interests
REVIEW RETURNED	02-Feb-2011

GENERAL COMMENTS	Your epidemiologist reviewer will probably demur re the small numbers. I still favour publication because of the honest way its presented-and potential importance

REVIEWER	***Ray Merrill*** Brigham Young University, College of Health & Human Performance
REVIEW RETURNED	17-Feb-2011

THE STUDY	The paragraph justifying the use of the logistic model is inaccurate in many ways. It needs to be more clearly stated that this is a descriptive, exploratory investigation. Bivariate analyses should be performed using the chi-square test. Use of the Mantel-Hanszel summary chi-square is questionable. The presentation of the frequency distributions should be accompanied with percentages. "Several grammatical errors"
RESULTS & CONCLUSIONS	The results need work according to the comments above. The tables need to be improved. Much of the Discussion needs to better tie the results to the literature. The message would be clearer if the paper was framed as a descriptive, exploratory study.
GENERAL COMMENTS	The title given to this study: “Association between Cancer and Contact Allergy- a linkage Study” is consistent with the main idea and purpose of the study. The study attempts to link allergies in relation to cancer using Denmark’s cancer and allergy registries. The main contribution of this study is that there has been little comparative study performed on this topic and this is the first study attempting to validate and publish the association between the two. The weakness of this study is evident by the information provided and stated by the authors: “studies focusing on specific chemical exposures are required to further increase our understanding of the role of contact allergies in the development of cancer.” An overall weakness of the paper is that the grammar is consistently faulty and

	often unnecessarily wordy. Grammar and language revisions are needed. Abstract Line 3, first sentence makes no sense. Remove the “a”. If the word limit allows, define contact allergy. The first two sentences of the Conclusions are Results. Introduction In the final sentence of the Introduction, simply say “This study will . . .” Methods I suggest combining the information in Tab1e 1 with the odds ratio information in Table 2 into a single table. In a footnote, put the note that the ORs are adjusted for sex and age (i.e., move from the title). It seems odd that cancer type is an independent variable, given that you are looking at the effect of contact allergy on cancer. I’d switch in your analyses. Then, interaction terms would involve sex, age and contact allergy. You do not need to give examples of what interaction terms look like. Note that this is a descriptive study design. As such, it exploratory and you may want to increase your alpha level to 0.1. Results Page 8, Line 21. Attach the test statistic p value to this statement about statistical significance. Page 8, Line 22. The sentence and reference belongs in the Methods where you talk about the population of study. Page 9, Line 3. Frequency distributions are typically accompanied with percentages. Page 9, Line 5. Is an OR = 1.1 of practical significance? I’d recommend using a Fishers Exact test to assess each cancer separately. Page 9, Table 2. I would include odds ratios for each of the cancer sites. Including the ICD codes in the table is not necessary. Also, why would you include them in Table 2, but not for all cancers in table 1; that is, why the inconsistency? Discussion Many ideas are presented in the first paragraph, with little development. Paragraph 2. It is not necessary to justify why you use logistic regression in this descriptive study here. Also, to say it is appropriate because you did it before is poor justification. The other reasons are problematic too. In short, this paragraph needs to be deleted. Page 10, lines 23-25 and first part of 26 are Results and do not add

	anything here. Delete. A single paragraph is needed that combines the limitations of this study. Several grammatical errors exist in the Discussion; for example, “The present study is unique in the sense that it is only possibly to perform . . .” “Different hypothesis have been suggested ...” The recurring theme that the results do not imply causality is obvious and over emphasized. Merely frame the study as a descriptive investigation and make this point about causality once.

VERSION 1 – AUTHOR RESPONSE

Dear Editor

We are very pleased with the reviewer comments, which have improved the manuscript markedly. We hope that it will now be acceptable for publication. We have addressed the following

Reviewer comments:

• The paragraph justifying the use of the logistic model is inaccurate in many ways. It needs to be more clearly stated that this is a descriptive, exploratory investigation.
○ Response: The manuscript is now described as a descriptive investigation (page 4 line 20)

• Bivariate analyses should be performed using the chi-square test. Use of the Mantel-Hanszel summary chi-square is questionable. The presentation of the frequency distributions should be accompanied with percentages.
○ Response: The percentages are now included in table 1. MH is used instead of the Fishers exact test, as they give the same p-value, while MH also gives a direction of the association. We find this extra information important as the analysis is used to study the possible hospitalization bias.
○ We will, if required, be ready to follow the reviewer recommendation.

• "Several grammatical errors"
○ Response: A professional British native language editor has revised the manuscript to minimize grammar faults etc

• Much of the Discussion needs to better tie the results to the literature.The message would be clearer if the paper was framed as a descriptive, exploratory study..
○ Response: Overall the discussion has been thoroughly rewritten and in the final sentence of the introduction the manuscript is mentioned to be a descriptive and exploratory investigation

Abstract
• Line 3, first sentence makes no sense. Remove the “a”. ,
○ Response: The sentence is changed to, “Contact allergy is a prevalent disorder. It is estimated that about 20% of the general population is allergic to one or more of the chemicals that constitute the European baseline patch test panel” (Line 3-4 page 4)

• If the word limit allows, define contact allergy
○ Response: Contact allergy is defined as a type IV allergy (line 6 page 4)

• The first two sentences of the Conclusions are Results.
○ Response: first two sentences have been deleted from the Conclusions

Introduction
• In the final sentence of the Introduction, simply say “This study will . . .”
○ Response: The final sentence is now changed to, “This is a descriptive exploratory investigation of the possible association between contact allergy and cancer by using cross-linkage between our contact allergy database and the national cancer database (the Danish Cancer Registry).”

Methods
• I suggest combining the information in Tab1e 1 with the odds ratio information in Table 2 into a single table. In a footnote, put the note that the ORs are adjusted for sex and age (i.e., move from the title).
○ Response: We have tried to combine the two tables. However, it turned out to become a very large table with difficulties in specifying the interaction terms. Therefore, we have retained the format with two tables. We will, if required, be ready to follow the reviewer recommendation but we believe this offers a more clear presentation of our data.

• It seems odd that cancer type is an independent variable, given that you are looking at the effect of contact allergy on cancer. I’d switch in your analyses. Then, interaction terms would involve sex, age and contact allergy. A
○ Response: Switching between contact allergy as the dependent and a specific cancer group as the dependent variable is an option. However, in our view it would complicate adjusting for various cancer groups as these may influence each other.

• Note that this is a descriptive study design. As such, it exploratory and you may want to increase your alpha level to 0.1.
○ Response: Increasing the alpha level to 1% is an excellent point in the view that it is an explorative study. However, it would not change the result as seen in table 2.

Results
• Page 8, Line 21. Attach the test statistic p value to this statement about statistical significance.
○ Response: The comment concerning the p-value seems to be referring to line 4-6. In the resubmitted manuscript this p-value is given on page 6 line 26-27

• Page 8, Line 22. The sentence and reference belongs in the Methods where you talk about the population of study.
○ Response: The sentence is now moved to page 5 line 16

• Page 9, Line 3. Frequency distributions are typically accompanied with percentages.
○ Response: The percentages are now included in table 1

• Page 9, Table 2. I would include odds ratios for each of the cancer sites. Including the ICD codes in the table is not necessary. Also, why would you include them in Table 2, but not for all cancers in

table 1; that is, why the inconsistency
○ Response: Table 2 has been changed to include OR for all of the cancer groups and the ICD codes have been deleted.

Discussion
• Many ideas are presented in the first paragraph, with little development
○ Response: Overall the discussion has been thoroughly rewritten

• Paragraph 2. It is not necessary to justify why you use logistic regression in this descriptive study here. Also, to say it is appropriate because you did it before is poor justification. The other reasons are problematic too. In short, this paragraph needs to be deleted
○ Response: The justification for using a logistic regression has been removed

• Page 10, lines 23-25 and first part of 26 are Results and do not add anything here. Delete.
○ Response: The sentences have been deleted A

• A single paragraph is needed that combines the limitations of this study.
○ Response: In the revised manuscript, the limitations are described from page 7 line 23 and onward.

• Several grammatical errors exist in the Discussion; for example, “The present study is unique in the sense that it is only possibly to perform . . .” “Different hypothesis have been suggested ...”
○ Response: A professional British native language editor has revised the manuscript to minimize grammar faults etc

• The recurring theme that the results do not imply causality is obvious and over emphasized. Merely frame the study as a descriptive investigation and make this point about causality once.
○ Response: The manuscript is now described as a descriptive investigation (page 4 line 20), and causality is only mentioned in the conclusion (page 9 line 12)