Author's response to reviews

Title: Serum concentration of alpha-1 antitrypsin is significantly higher in colorectal cancer patients than in healthy controls

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Version: 9
Date: 12 May 2014

Author's response to reviews:

May 12, 2014

Dear Ms. Cherry Battad,

Our additional 'tracked changes' file has been removed from additional files, as required.

We hope that you will find this new version suitable for publication.

Best wishes,

S. Pérez-Holanda F.

You provided a covering letter for the most recent version of this manuscript on 6 May 2014:

MS: 5507296681148823

Research article:

Alpha-1-antitrypsin serum levels and protease inhibitor phenotypes distribution. Case-control study in colorectal-cancer patients

Sergio Perez-Holanda, Ignacio Blanco, Manuel Menéndez, and Luis Rodrigo

BMC Cancer

Answers to Editors and Reviewers

06/05/2014:

Dear Ms Cherry Battad:
We would like to first thank the Editorial Board and the Referees for their interest in evaluating our manuscript, as well as for their valuable suggestions and useful ideas for improving our paper.

In accordance with your request, we have copyedited the paper to improve the style of written English, and included funding sources for this study in acknowledgements sections.

Also, as required, we have rewritten and restructured the manuscript.

We hope that you will find this new version suitable for publication.

Yours sincerely,

Perez-Holanda, S et al.

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25/04/2014:

Dear Ms Cherry Battad:

We would like to first thank the Editorial Board and the Referees for their interest in evaluating our manuscript, as well as for their valuable suggestions and useful ideas for improving our paper.

In accordance with your request, we are sending the marked copy of the manuscript with the title, text, references and deleted tables labeled and highlighted in red, and everything new in blue.

Also, as required, we have rewritten and restructured the manuscript.

We hope that you will find this new version suitable for publication.

Yours sincerely,

Perez-Holanda, S et al.

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14 April 2014:

Dear Editor,

We would like to thank the Editorial Board and the Referees for their interest in the evaluation of our manuscript, as well as for their valuable suggestions and useful ideas to improve the quality of our paper.

Please find below the issues raised by the two reviewers, and our point-by-point responses.

Reviewer 1:

1). Abstract: In the results section change Pi*S nor Pi*Z.

Answer: The requested change has been made.

2). MATERIALS AND METHODS: Have you considered performing IHC for AAT to document expression (or even overexpression in tumor)?

Answer: The initial aim our study was to analyze the prevalence of AAT deficiency in patients with colorectal cancer from our geographic region. We had not thought about doing this, but we now realize would be good to examine in future studies.

3). DISCUSSION: Could AAT levels be correlated with stage?

Answer: Highly significant differences were found when comparing the mean serum concentration of AAT from the CRC group (in total and by TNM subgroups) vs. Controls. However, the comparison of the mean value of the whole CRC group vs. each of the CRC stages (I, II, III and IV) separately revealed no significant differences between them (p=0.502). These data are now summarized in a new table (Table 5).

4). DISCUSSION: Outcomes?

Answer: Patients were recruited over 4 years (2008 to 2012), and there were large fluctuations in the number of cases collected each year. Consequently, the follow-up time of patients was highly dependent on the date they were recruited, and this has been very variable. Thus, patients recruited at baseline were followed for about 3-4 years, but those recruited in the subsequent years were
followed for a shorter time (e.g., the last to be recruited had a follow-up of only a few weeks or months). Of several cases detected before the start of the study, some of them died but other were controlled. In the future, we would need to double the number of cases and follow them up for several years to be able to analyze their clinical course.

5). TABLES: Perhaps reformat tables as that they are wider and thus have less less. This may make it easier to read.

Answer: We have tried to improve the appearance of the tables. We also deleted the old table 5, "Serum Concentrations of Alpha-1 antitrypsin for the different Pi * Genotypes AAT ...", since it was very theoretical and probably of interest only to those skilled in interpreting AAT data. It has been replaced by a new small table (Table 5) that illustrates the "Comparison of Serum Concentrations of AAT in the group of patients with colorectal cancer (total and classified by TNM stages) vs. Controls".

Reviewer 2:

1) We understand that this reviewer believes that the discussion and conclusions are not properly balanced with the reported data, and that the title does not correspond with the findings. Therefore, she recommends changing the title and reworking the discussion section. She also considers of interest to compare AAT levels with the severity of the disease instead of AAT phenotypes.

Answer: We believe that this reviewer's comments are absolutely valid, and are grateful for them. We believe the change in the title marks a significant improvement in our paper.

Therefore, we have changed title to: “Serum concentration of alpha-1 antitrypsin is significantly higher in colorectal cancer patients than in healthy controls”.

2) Discussion. The first paragraph is repeated like in the introduction.

Answer: We agree; this paragraph has been deleted.

3) Discussion. For the start of discussion would be better sentence from page 11, “The only statistically significant finding in this study was the markedly higher AAT serum concentrations in CRC subjects compared to HUP controls, regardless of their Pi phenotype were normal (MM) or deficient (MS, MZ and SZ)”

Answer: We agree, and we have made this change in the new version of the paper.
4) Authors shell focus on the findings and significance. I recommend totally rework Discussion section.

Answer: We agree, and we have done this in the new version. We have rewritten much of the discussion, so that it now focuses more closely on the meaning of the findings, while eliminating many theoretical concepts of alpha-1 antitrypsin that we assume are well known by those who are familiar with this field of interest. These changes have included the removal of the old Table 5, and its replacement by one that summarizes some of the important findings. For this reason, we have had to cite a substantial number of studies about serum AAT in CRC and other tumor types, as well as several references about expression of AAT in tumor tissues, etc.

We hope that, having made these changes, that you will now consider this manuscript to be of interest to your readership and suitable for publication in BMC Cancer.

Yours sincerely,

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