Author's response to reviews

Title: Environment And Genetics in Lung cancer Etiology (EAGLE) study: a novel population-based integrative case-control study of lung cancer

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Author's response to reviews:

Dear Dr. da-Silva,

We are grateful for the reviewers¿ comments, and provide here below our responses.

Please, note that we have slightly shortened the manuscript title and added an author, Dr. Ilona Linnoila, among the authors (by mistake we had originally listed her in the acknowledgments).

We would be happy to provide more details on any of our responses, should you have any questions.

Thank you for your consideration.

Sincerely,

Maria Teresa Landi, MD PhD

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Response to Reviewer #1:

The purpose of this manuscript is not to address the effects of tobacco smoking on lung cancer, rather to give a detailed description of a complex study design based on an innovative integrative approach.

For years, epidemiologists have spoken about integrative designs, and this study represents possibly the first comprehensive example in practice. Since EAGLE main goal is to do integrative analyses including molecular markers, epidemiological data, genomics results and clinical endpoints, we need to describe all the study components to illustrate the design. A study on the association of tobacco smoking and lung cancer risk would require much more sophisticated analyses and the related description and discussion would leave no space to illustrate this complex design. We reported some results on the association between tobacco smoking and lung cancer risk simply to show the integrity of our data collection and as an example of the many analyses that can be performed in EAGLE. In the future, we plan to integrate these results with data on gene expression changes by smoking and their related effect on survival.

As the reviewer pointed out, we view this manuscript as the fundamental reference for all EAGLE analyses to come, both in descriptive epidemiology and genomics. Consequently, we retained the discussion on the integrative approach, which is fundamental to the manuscript. Similarly, the description on the biospecimens is critical because biospecimen collection is a key component of the study design, and affects study management and participation rate. However, to respond to the first reviewer¿s comments, we did shorten the description of the genomics analysis, biospecimens processing, and bioinformatics infrastructure, and deleted the related figures, as he suggested. Moreover, we added more results and discussion on the risk of lung cancer by inhalation of

cigarette smoking and pack years, also separately for men and women, as requested by the reviewer. We are planning a subsequent paper to address the role of tobacco smoking in lung cancer risk more in depth, including potential differences on susceptibility to tobacco smoking¿s effects between men and women. EAGLE benefits from a population-base design with high participation rate and we obtained basic information on smoking also from subjects who refused to participate in the study. Moreover, information on smoking habit by gender in the catchment area can be estimated from the controls and we plan to collect information on age and sex in the catchment area through the census data. In the future, we plan to estimate exposure and demographic characteristics in the entire study base, allowing calculations of absolute lung cancer risks associated with smoking separately for men and women, to address this question.

Abstract conclusions: As explained above, we feel that the conclusions are relevant to the main goal of the manuscript, which is to illustrate the integrative design of EAGLE and its utility. We have also added a sentence on the tobacco smoking-lung cancer risk association to reflect the added data as suggested by the reviewer.

Information in additional file 1: we have incorporated this information in the main manuscript (from end of page 10 to beginning of page 13) as suggested.

p13-14 in the original version: As stated above, we have kept the information on biospecimen collection, but we have reduced the description on specimen processing and deleted the relevant flow chart. We have also substantially reduced the bioinformatics and management description, and merged them into a single section (end of page 13 and beginning of page 14), and deleted the related figure.

p15 in the original version: we agree with the reviewer. We have added data on the completion rate (ratio between participants and those we contacted by sending the invitation letter, including those that remained untraceable) (last section of page 17)

p16-18 and p19-20 in the original version: As stated above, we have retained the discussion on the integrative design, which is the main goal of our manuscript, but shortened the discussion on biospecimens and genomics as suggested. Moreover, we have added results (end of page 18 and beginning of page 19), discussion (pages 21-22) and Tables (Tables 5 and 6) on the association of lung cancer risk with tobacco smoking.

Table 1: since it describes the completeness of questionnaire and biospecimen collection, which are integral part of the study design, we have retained this table.

Table 2: we have added information on the table footnote on the RR methodology. The footnote now says: ¿Rate Ratio corresponding to Risk Ratio (rates were calculated as cases/(population*2.86 years of study duration))¿.

Tables 5 and 6 in the revised version: As suggested, we have added data on lung cancer risk by pack years of tobacco smoking and smoke inhalation overall and separately by sex.

Table 5b in the original version (currently Table 7b): We have added confidence intervals to the population attributable fractions, as requested, using the method proposed by Greenland and Drescher (1993). We reported the proportion of cases exposed to smoking to show the difference by histology and to calculate the PAF. The proportion of controls at each smoking level is found in Table 4 of the revised version.

Table 6a and 6b in the original manuscript: these tables have been deleted, and results summarized in the text (last paragraph of the Results, page 19) as requested.

Figures 1 and 2 in the original manuscript: as suggested, we have omitted these figures.

Reviewer #2.

We are happy to see that the second reviewer appreciated the first version of our manuscript. Although we tried to follow suggestions from the first reviewer, we attempted to keep the original flavor of the manuscript, as it was approved by the second reviewer.