Author's response to reviews

Title: Identification of low penetrance alleles for lung cancer: The GEnetic Lung CAncer Predisposition Study (GELCAPS)

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Author's response to reviews: see over
Dear Sir,

**MS:1969620475172601: Identification of low penetrance alleles for lung cancer: The GEnetic Lung CAncer Predisposition Study (GELCAPS)**

Thank you for providing us with an opportunity to submit an amended manuscript. Our paper has been revised to address the two reviewers comments. Specifically:

**Reviewer 1: Ulla Vogel**

1.1. The control group should also be described in a table, and it should be assessed how they deviate from the general population with regards to fx smoking and it should be described how they differ from cases (apart from the lung cancer diagnosis).

Response: Details of the control group are now presented in a revised Table 1.

2. In table 1, % should be added to histology and tumor stage.

Response: As requested percentages have been provided for histology and tumor stage.

3. I don't understand why clinical details and outcome was only collected from a subset of the cases. This study is very well suited for studying interaction between genetic variation and lung cancer treatment in relation to survival. Moreover, you do not have the problem with the different sex-ratio among cases and controls.

Response: To date we have only collected survival data on a subset of cases. It is our intention to collect complete data on this from all cases using the NHS central registry. This is an ongoing initiative and this is now stated in the text.

4. You have to discuss the implication of the different sex-ratio among cases and controls and to show the age distribution among controls. Does that match the one for cases ?

Response: The implication of the sex difference between cases and controls is discussed. Data on the gender of controls is presented in the revised paper.

5. Legends for fig 1 and 2 are mixed up. In fig 1, I do not understand the y-axis, is that total numbers of recruited persons ? Why does it go up to 7500 if it is only patients as stated in the legend?

Response: Typographical errors relating to labeling of Figures 1 and 2 have been corrected. The Figure relating to accrual capture both cases and controls- this has been clarified in the revised manuscript.

6. It is not clear to me whether DNA has been purified from the blood samples or not. State that clearly.
Response: It is now clearly stated that DNA has been extracted and quantified from the EDTA blood samples. Details of this and quality control issues relating to DNA are now included in the text. Furthermore, included in the text is reference to the use of this resource to identify a novel lung cancer variant on chromosome 15q (Nature Genetics in press).

7. You might want to describe the procedure if other researchers would like to have access to the samples, is it possible; does it have to be approved by a board?

Response: This is under review currently.

8. In the first few lines, it is stated that ‘the disease is frequently cited as a malignancy sole attributed of environmental exposure’. Why not mention smoking explicitly?

Response: The introduction has been re-edited to explicitly mention smoking as a risk factor for lung cancer.

Reviewer 2: Emanuela Taioli

2.1. The description of this large effort is interesting, and would contribute publicity to the study. However, several details are missing. For example, how many patients refuse to participate, and what was their profile in terms of age and gender? It is not clear why parterns are chosen as controls. Given that the cases are mostly smokers, the partner are likely exposed to passive smoking. Is this information collected? it is important that table 1 includes such data. The only analysis reported, i.e. survival, is not adjusted for year of recruitment or other important factors such as therapy, age at diagnosis etc. This is a mandatory step.

Response: As the ascertainment of cases and controls was conduced through a national network whose remit is to facilitate participation in clinical trials data on invitation compliance is not collected. On the basis of our intimate knowledge of a restricted numbers of centers compliance is ~70%. As stated in the text purely for practical reasons we choose to collect samples from spouses and partners of cases. We have included data on controls in a revised Table 1. As requested comparison of survival according to stage at presentation has been adjusted for covariates. Unfortunately we have not sought to collect data on passive smoking. As stated in the text the primary aim of the initiative was to assemble a resource to search for main genetic effects and gene-gene interaction. It is acknowledged that evaluation of gene-environmental effects is best conducted in the context of other studies ideally ones derived from population-based cohorts. The discussion includes commentary on this area with reference to one of the main population-based cohorts.

2.2. It is not clear what the contribution of female controls will be. There is a vague explanation of the future plans, but it is not convincing.

Response: The sex of controls ascertained through initiatives such as GELCAPS will usually be of the opposite gender to cases, and controls are potentially over-matched with respect to many lifestyle risk factors. Theses limitations can be offset to a large degree by using samples collected from the healthy spouses/partners of one cancer as a source of controls for a different cancer. This is something we are currently pursuing with respect to a similar NRCN sponsored initiative the National Study of Colorectal Cancer Genetics (NSCCG). This is discussed in the revised text.

2.3. The literature is outdated. There are several meta analyses on genes/lung cancer, for example at least two on GSTM1 and lung cancer, that are not mentioned. This reference list has to be updated.
Response: We acknowledge this deficiency and have updated our referencing relating to this component of the text.

We are grateful to the two reviewers for their helpful comments and having made the above changes to our paper we hope that it is now suitable for inclusion in BMC Cancer.

Yours sincerely,

[Signature]

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