Author's response to reviews

Title: Polymorphisms in xenobiotic metabolizing genes (EPHX1, NQO1 and PON1) in lymphoma susceptibility: a case control study

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Author's response to reviews: see over

Reviewer: Kathryn Barry

Reviewer's report:

Major Compulsory Revisions:

1. The Abstract still notes a stronger association for PON1 rs662 in males than females. Even though the p-value for males is lower, the OR point estimates for
males and females are relatively similar. In addition, the confidence intervals for males and females are very wide and each includes the point estimate of the other group. Please remove the point about a gender difference from the Abstract and elsewhere in the manuscript as well (Results and Discussion).
AR: Following the reviewer’s suggestion, all references in the manuscript highlighting gender-associated differences has been removed.

2. Now that the focus of the paper is on main effects of genetic variants and NHL risk, please add some citations of genome-wide association studies (GWAS) for NHL in the Background section, for example Smedby et al, PLoS Genet 2011 (for follicular lymphoma specifically) and Vijai et al, PLoS Genet 2013. Were the SNPs studied in the current analysis included in the GWAS scans? If so, could you please add some justification to study these variants again here? One potential justification could be to study these variants in an exposed population, although the limited exposure assessment and potentially heterogeneous nature of the exposures here should again be noted.
AR: The results from GWAS studies and a discussion have now been included and commented in the discussion by adding the following paragraph:

“Recent genome-wide association studies (GWAS) have identified polymorphisms associated with lymphoma risk such as rs10484561 [39], rs2647012 [40] and rs6457327 [41] in the human leukocyte antigen (HLA) region on 6p21.32 and 6p21.33. Very recently, a novel region on 11q12.1 showed also association with lymphoma susceptibility [42]. Interestingly, none of these polymorphisms seems to lie on xenobiotic metabolizing genes. At this point, it is important to take into account that lymphomagenesis is a multifactorial process, and genetic-determined suboptimal xenobiotic metabolizing machinery could partly explain not all lymphoma cases but some of them, which have developed under certain exposure conditions. Geographical restriction of cases and controls is not a common feature of GWAS and, despite their undoubted utility in assessing the genetic determinants of the diseases, this approach could hamper the understanding of the contribution of xenobiotic exposure to lymphomagenesis.”

3. In the Discussion section, there is currently not enough focus on NHL or hematological outcomes and rather attention on other cancers, for which the etiology may not be relevant to NHL. Please incorporate some mention of the NHL GWAS studies (and any other studies that considered these SNPs with respect to NHL) in the Discussion. Suggest also adding more papers that investigated the SNPs in relation to hematological outcomes, for example, for NQO1 rs1800566: Wan et al, EHP 2002; Chen et al, Xenobiotica 2007; Sun et al, Carcinogenesis 2008; and Lan et al, Science 2004.
AR: Focus on studies dealing with genetic susceptibility in haematological tumors has now been given and consequently the references dealing with
non-hematological tumors have been deleted.

Discretionary Revisions:
1. In the concluding sentence of the Abstract, please give the rs number for the PON1 SNP. Even though it is given earlier in the Abstract, it should also be mentioned with the genotype. Please also state the rs numbers for the respective SNPs in Tables 2-4.
AR: This correction has been made.

2. Suggest presenting only one genetic model in Table 2 and mentioning in the text that results were similar with the recessive and co-dominant models. Suggest presenting recessive here to be consistent with Table 3 (or present the co-dominant model in both tables). Please also justify in the Statistical Analysis section of the Methods why you chose the recessive model as the main model for the paper.
AR: The text has been modified accordingly. The following paragraph has been added in the Methods:
“Given that xenobiotic metabolizing enzymes would behave as possible tumor suppressor by eliminating potential carcinogens, a recessive model for the p-value calculation was preferred although the main results were also studied following dominant and co-dominant models”.

3. Suggest changing “genetic profile analysis” to “joint effects analysis” in Table 4 and throughout the text of the paper since the term genetic profile has some connotations of a large-scale analysis, whereas here three SNPs were studied.
AR: The reviewer’s suggestion is pertinent and the text has been modified accordingly.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.

Reviewer: Pierluigi Cocco
Reviewer’s report:
The authors complied with all the comments I raised.
Minor essential revisions:
Page 6, line 2: replace "TT 12.5%" with "CC 12.5%".
AR: The text has been modified accordingly

Discretionary revisions:
Page 9, lines 1-2: "This could be related to gender-related differences in PON1 activity [reviewed in 40]."
This reviewer would suggest to consider also the different prevalence in relevant occupational exposures between the two genders as a plausible explanation of the stronger association observed among males.

AR: Following reviewer 2 suggestion the finding about possible gender-associated differences has been deleted from the manuscript and therefore now there is no need for such explanation.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.