Reviewer's report

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

Version: 2 Date: 11 February 2013

Reviewer: Pierluigi Cocco

Reviewer's report:

The revised version of this paper matches some points this reviewer raised on the original submission, but not the major point, which was the inadequacy of the study design to pursue the aim of assessing the interaction between polymorphisms in metabolic genes and occupational and environmental exposures in affecting risk of lymphoma. As stressed in the previous review, selection bias from the source of the controls (all were blood donors, and therefore not an unbiased sample of the general population) makes results based on the questionnaire information invalid. Another non amendable problem is the extremely generic type of information that was collected and analyzed. The conclusion is therefore unwarranted that subjects carrying the PON1 GG genotype would be at greater risk of lymphoma if residing in proximity of an industrial area, where, based on the list of the plants reported in the Methods section, there is no indication of a specific pollution from organophosphate insecticides, the major substratum of that gene.

From this revised version, we learn that the source of cases was heterogeneous, which might also have lead to changes in the geographical distribution of their residences in comparison to the blood donors, possibly resulting in an artifactual concentration of the observed excess of the PON1 GG genotype among the residents in proximity to the industrial area. Besides, source heterogeneity, in space and time, was apparently the reason for the low proportion of questionnaires available for the cases, which would make it difficult to generalize the results to all lymphomas (the old follicular lymphoma cases were all presumably excluded, although the authors are not explicit about this).

Major compulsory revision

I would suggest the authors to concentrate their report on the metabolic gene polymorphisms, which are of interest per se, and to drop the questionnaire part of their paper, which would have required a specific study design instead of a post hoc assembly of generic data from heterogeneous sources. Following this reviewer’s suggestion, they might make full use of the whole study population, presenting the analysis by gender; a subgroup analysis by smoking might also still be acceptable, and the conclusion of the association of polymorphisms of genes implicated in xenobiotic metabolism on lymphoma risk still relevant, as the explored genes would not affect risk if not through the metabolic changes they induce in their substrata.
Minor essential revisions

1. Refer to the 2008 WHO classification of Lymphoma, and not to the “WHO book”.
2. The Bonferroni correction would not be necessary; the sentence “This association was restricted to males (p= 0.008), but not present in females (p= 0.05) “ is unjustified. Risk is elevated in both genders, and a formal test of heterogeneity would most likely suggest their consistency.
3. In the discussion, please describe honestly the source of cases and controls as a limitation.
4. Please, do not tediously repeat the percentage frequency of each genotype in the text; briefly refer to what reported in the tables.
5. This reviewer understands that another peer suggested to explore the gene-gene interaction, but what was the rationale for the “haplotype analysis” needs to be explained in the discussion. Was there any published report suggesting LD between the polymorphisms investigated in this paper? Also, a haplotype is defined as a combination of alleles at adjacent locations on the same chromosome that are transmitted together, or are statistically associated. The SNPs herein investigated are located in chromosome 1, 7, and 16; therefore, the authors should use the term “gene-gene interaction” to define the analysis they conducted.
6. Have the text revised by a native English expert in scientific language.

Level of interest: An article of limited interest

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