Author's response to reviews

Title: HFE C282Y and H63D in Adults with Malignancies in a Community Medical Oncology Practice

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PDF covering letter
Dear Dr. Puebla:

Thank you for the prompt and thorough review of our work. Herein we have summarized responses to the criticisms and suggestions of the third Reviewer, and offer point-by-point responses. We had apparently overlooked this Reviewer 3’s critique when we first submitted revision of this paper in November. The criticisms and suggestions are displayed in italics, and our responses appear in standard font. We have largely excluded the commentary of the Reviewer that does not contain suggestions for change.

**Reviewer 3: Victor Kiri**

The authors referred to an apparent age-related susceptibility to malignancy in persons with C282Y (accredited to a previously published study), which they claim was contrary to their findings. However, I am not convinced that theirs was designed sufficiently enough to discount possible age effect. The claim that there was no bias that favored selection of patients of a certain age because “the present cohort of patients consisted of consecutive patients with malignancy who were evaluated in a community medical oncology practice” was clearly not sufficient. This was an observation study and not a controlled trial. As such, if age is a possible confounder or indeed, if you wish to eliminate age as a factor, then the correct approach is either to adjust for age in the analysis (i.e., stratification) or match controls to the patients with malignancy.

We have removed the statement about unbiased selection of the present cohort, and simply described briefly the circumstances under which they patients were recruited for the study. We removed statement that refuted a hypothesis of others that there may be increased age-related susceptibility to cancer among persons who inherit HFE C282Y. Thirdly, we inserted an additional reference describing a meta-analysis of five survival studies of persons with hemochromatosis and C282Y (Waalen et al., 2003). This demonstrates further that the frequency of the C282Y allele is constant or nearly so at all ages. Thus, we have formulated this new paragraph as the first of the Discussion: “The present 100 consecutive adult patients with malignancy were 12 years older than the 318 control subjects, on average, yet the corresponding frequencies of \textit{HFE} C282Y and in the patients and in control subjects were similar. This is consistent with most studies that demonstrate that the frequency of the C282Y allele is constant or nearly so at all ages (22; 22a). The corresponding frequencies of \textit{HFE} C282Y and H63D in the patients and controls were also similar. Overall, the occurrence of C282Y or H63D was not associated with an increased (or decreased) OR for malignancy in the present study. Nonetheless, the present observations do not exclude the possibility that an increased (or decreased) risk of developing specific types of malignancy may be associated with common \textit{HFE} mutations.”
We have also added a new reference which demonstrates that there is a positive association of C282Y and lung cancer in women (but not men). This paper by Rodriguez-Paris et al. (2003) has been cited in the Background (first paragraph) and Discussion (fourth paragraph) sections. In the Discussion, we also added this sentence: “In a recent study, the prevalence of C282Y in women with lung cancer was significantly greater than that in men with lung cancer or in control subjects with head and neck cancer [Rodriguez-Paris et al., 2003].”

These additional references were cited at appropriate points and included in the Reference section.


We believe that these changes comply with the suggestions of Reviewer 3, and have significantly improved the manuscript. Each author has reviewed the manuscript and agrees with the changes. We have also reviewed the manuscript to be certain that formatting is correct in accordance with the on-line checklist. Thanks in advance for your further review of our work.

Yours truly,

Ronald T. Acton, Ph.D.

cc: J.C. Barton, L.F. Bertoli