Reviewer's report

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

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Reviewer: Anna Carla C Goldberg

Level of interest: A paper of limited interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

The manuscript: HFE C282Y and H63D in Adults with Malignancies in a Community Medical Oncology Practice by James C. Barton, M.D., Luigi F. Bertoli, M.D., and Ronald T. Acton, Ph.D., refers to a study of 100 unrelated cancer cases that have been genotyped for the two most common Caucasian mutations of the HFE gene. The authors try to identify if iron metabolism diseases could be linked to cancer within a consecutive sample of patients with different types of malignancies, hematologic or otherwise. The question is not new but the authors try to shed light on a controversial subject by expanding the types of cancer analysed. The method and statistical analyses used are clearly stated, and the control group is adequate. As the authors are American, their English is of course impeccable.

Discussion

Minor point:

It strikes us that, for example, in the 6 cases polycythemia vera, apparently 4 carried one of the mutated alleles. The data are not clear on this point.

Major points:

In another part of the discussion, lower frequency of H63D mutation is associated to B lymphoma but p = n.s.. In other cases, no difference is seen when compared to normal controls. As the authors themselves propose:

The allele frequencies of C282Y and H63D in the central Alabama whites are relatively great (0.0896 and 0.1447, respectively) [15, 16]. Thus, a positive or negative association of malignancy with HFE genotype in a population in which the frequency of HFE mutations is relatively high may be due to chance association with other genetic or environmental factors. Contrariwise, a significantly increased relative risk of malignancy may be more readily demonstrated in populations in which C282Y or H63D frequencies are lower.

Thus, in spite of a very well written and detailed discussion, the general impression conveyed is that HFE gene might indeed have a role in development of malignancies, which cannot be concluded
from the data. The authors regard the O.R. values that are over 2 or under 0.5 as having relevant biological value or in other words, that they represent a trend (results and discussion). However, in no instance the results are statistically significant which compromises the first sentence of conclusions as stated in the abstract:

Conclusions
In adults, C282Y or H63D may influence the risk of developing certain common malignancies. Study of more patients with common types of malignancies is needed to determine if trends described herein would remain and yield significant differences.

Thus, discussion and conclusions should be changed accordingly as they are indicative that even in an extended cohort of 100 patients HFE gene is not conducive or associated to cancer development.

Competing interests:

None declared.