Reviewer's report

Title: Hepatocellular carcinoma and the penetrance of HFE C282Y mutations: a cross sectional study.

Version: 1 Date: 14 March 2005

Reviewer: Arne Åsberg

Reviewer's report:

General
The authors have analysed tissue biopsies from hepatocellular carcinoma patients for HFE mutations. Using the numbers of HFE C282Y homozygotes in this population and in control populations from other studies they have estimated the relative risk of hepatocellular carcinoma in HFE C282Y homozygotes. Furthermore, the authors have estimated the lifetime risk for hepatocellular carcinoma in HFE C282Y homozygotes. Their population of cases is relatively large, and their reasoning is basically sound.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The proportion of HFE C282Y homozygotes diagnosed with hepatocellular carcinoma depends heavily on care of these individuals, i.e. whether they are diagnosed with hemochromatosis in the precirrhotic stage and properly followed up. The authors do mention that the population is "well-defined" and that "only a small proportion of HFE C282Y homozygotes have been diagnosed and treated for haemochromatosis". Still, they "found little evidence of undiagnosed haemochromatosis-related HCC". As this is a crucial point in generalizing their findings to other populations, the authors should more explicitly discuss their findings of penetrance in relation to the area's health care for hemochromatosis patients in general, and whether the 6 cases with known hemochromatosis were properly treated in the time period before they were diagnosed with hepatocellular carcinoma.

As a measure of relative risk the authors have used the proportion of HFE C282Y homozygotes in the population of hepatocellular carcinoma men (8/102) divided by the proportion of HFE C282Y homozygotes (men and women) in the control population (9/1508). This is not an ordinary measure of relative risk. In this respect, the study is a case-control study, so the proper measure of relative risk is the odds ratio.

The authors state "Our results show that the frequency of HFE C282Y homozygosity in the male HCC cohort was 13 times higher than that in the control cohort the HFE C282Y homozygous genotype is therefore a significant cause of liver cancer." Association is not a proof of causality, so this sentence is better changed.

The first sentence in "Histology" in "Results" should refer to Table 3 instead of Table 2.

The term "HCC" is explained in Table 3 but not in Table 2, and the terms "Stage" and "Grade" are not explained in Table 3.

Discretionary Revisions (which the author can choose to ignore)
Some repetitions of results appear in "Discussion".
The last sentence in "Histology" in "Results" could be moved to "Methods".

**What next?:** Accept after minor essential revisions

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

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests