Reviewer's report

Title: CHEK2 1100delC is prevalent in Swedish early onset familial breast cancer, a case control study

Date: 16 April 2007

Reviewer: Peter Devilee

Reviewer's report:

General

This manuscript describes the prevalence of the CHEK2*1100delC variant in a population of breast cancer cases, part of which were selected for having a family history for the disease. The variant appears to be enriched among patients with a family history, particularly those with a young age of onset.

Major Compulsory Revisions

These findings are largely confirming previous work by a number of other teams. While relevant for the Swedish population, it would be interesting to know if there were any other interesting observations made. In particular, there have been claims that heterozygous carriers are at increased risk to develop recurrences or second primaries, and these data have been collected on at least one cohort.

On patient selection: both the familial risk cohort and population-based cohort were counter-selected for BRCA1/2 mutation carriers, but it seems the familial cases were better investigated for the presence of mutations than were the incident cases. This should be specified in more detail: what has been tested in each cohort? This is relevant because it has been suggested that prevalence of CHEK2 is particularly low among BRCA mutation carriers.

It is not clear to me on what grounds the population-based cohort is called exactly that. In fact, these were incident cases at two local hospitals in a small time interval, and are therefore more appropriately called hospital-based cohorts.

From an epidemiological viewpoint, the subdivision of the familial cases into high risk and low risk on the basis of the number of 1st and 2nd degree relatives with breast cancer is somewhat cumbersome. The relative risks are determined by both number of cases as well as their age of onset. Thus a patient with two 2nd degree relatives above age 50 could have the same relative risk as patient with one 1st degree relative below age 50. It would be more appropriate therefore to apply the Claus-model (or any similar other model which takes both factors into account) to compute the risk for each proband, and then subgroup the probands from low- to high-risk accordingly.

Technically, detecting 1100delC in CHEK2 can be tricky because of the many pseudogene copies. What have the authors done to confirm that their carriers have the 1100delC in the functioning gene copy?

Minor Essential Revisions

In tables 1a and 1b, it is not clear what comparison the p-value is reflecting.

What next?: Accept after minor essential revisions

Level of interest: An article of limited interest
Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

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