Reviewer’s report

Title: Five recurrent BRCA1/2 mutations are responsible for cancer predisposition in the majority of Slovenian breast cancer families

Version: 2 Date: 21 July 2008

Reviewer: Patricia Tonin

Reviewer’s report:

The authors have satisfactorily addressed the comments.

Minor Essential Revisions:

Suggested editorial revisions are indicated below:

ABSTRACT section:

Background: “The current study was aimed at establishing the mutation spectrum of BRCA1/2 in the …”. There is no need to write the BRCA1/2 and genes when “BRCA1/2” suffices.

Methods: “The original population database was composed of cancer patients from the Institute of Oncology Ljubljana in Slovenia which also includes current follow-up status on these patients.”

Methods: “The inclusion criteria for the BRCA1/2 screening were: (i) probands with at least two first degree relatives with breast and ovarian cancer (ii) probands with only two first degree relatives of breast cancer where one must be diagnosed less than 50 years of age; and (iii) individuals patients with…..”

Conclusion: “A high mutation detection rate and the frequent occurrence of a limited array of recurring mutations facilitates BRCA1/2 mutation…”

BACKGROUND section:

First paragraph:

“A family history of breast and/or ovarian cancer is the most important risk factor for the development of these diseases [or cancers].”

First paragraph:

“The first step in implementing a BRCA1/2 genetic counseling program that includes mutation screening and then carrier detection in families found mutation-positive, was …”

Last paragraph:

“The aim of our study was to assess: (i) the nature of BRCA1/2 mutations
found and (ii) the cancer phenotype...

METHODS section:

Patient and families in first paragraph: “This study was performed with families residing in Slovenia, and more specifically those followed at the...” Also, I suggest you remove clause “as suggested by the high degree of ethnicity in the general population” as this issue is dealt with in detail later in the Discussion section.

Patient and families in second paragraph: Perhaps edit inclusion criteria as suggested in changes described above for the Abstract?

Patient and families in fourth paragraph: I suggest you move this paragraph describing details of mutation detection to the following subsection ‘Mutation screening’.

RESULTS section:

BRCA1 mutation analysis subsection:

“Several mutations were found repeatedly in different families. These include the 1806C>T BRCA1 mutation found in 10 families and reported previously in our population [6]; and the 5382insC BRCA1 mutation found in 5 families, which is the second most common reported mutation found worldwide. The 967ins7 mutation was found in three families.”

Mutation detection rate subsection:

“Although more families need to be investigated..., the probability of finding a mutation correlated numerically....”

“However in families with ovarian cancer ...was found in 24/46 (52%) of families with less than four affected members and in 7/14 (50%) families with greater than three affected members...

Cancer phenotypes in families.....:

I would argue that the mixed inclusion criteria also confounds attempts to properly assess genotype-phenotype correlations; and thus “The sample size and mixed inclusion criteria does not permit an accurate assessment of genotype-phenotype correlations, however some trends could be observed.”

In the same subsection, what is “CI,40.1-45.8”? Is this the age range if so what does CI mean as it implies confidence intervals?

“It is noteworthy that in our series the average number of breast cancers .....(3.3) as compared...”

DISCUSSION section

Second paragraph:
Check if you indeed mean “defective” in “Adequate proband-based information dissemination in a proband mediated model…”

Third paragraph:
“Since we often face genetic counselling…”
“The intake criteria we employed thus seemed adequate…”
“It is also possible that with our mutation screening…and thus we have a lower estimate…”

Fourth paragraph:
“It is known and was also observed…that the best MDR were obtained..”

Sixth paragraph:
“Four distinct types of mutations…in 67% of the BRCA1/2 mutation-positive families.”
“Therefore the genetic screening was initiated with the detection of these four particular..”

Paragraph 10:
“Indeed, all three most common mutations…segregate in Italian and Austrian families” [Alternatively “…segregate in families from Italy and Austria”].

TABLE 1 and ADDITIONAL FILE:
Customary to refer to cancer of the uterus or uterine cancer rather than ‘uteri’.
What is ‘colli uteri’?

Discretionary Revisions:
None

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

Quality of written English: Acceptable

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.