Reviewer's report

Title: Implication of Xenobiotic Metabolizing Enzyme gene (CYP2E1, CYP2C19, CYP2D6, mEH and NAT2) Polymorphisms in Breast Carcinoma.

Version: 1 Date: 24 October 2007

Reviewer: Valentina Paracchini

Reviewer's report:

General
The present paper describes a case-control study on 314 breast cancer cases and 246 controls selected from the population living in Sousse, and investigates the association of XME polymorphisms and breast cancer. The Authors consider the potential contribution of the combined multilocus genotypes in breast cancer susceptibility, and they analyze the association of XME gene variants with tumor pathological characteristics, with survival and relapse after treatment.

The authors found that the mEH (C/C) mutant and the NAT2 slow acetylator genotypes were significantly associated with breast carcinoma risk ($p= 0.02$; $p= 0.01$). For NAT2 the association was more pronounced in postmenopausal patients ($p= 0.006$). In addition, a significant association between CYP2D6 (G/G) wild type genotype and breast cancer risk was found only in postmenopausal women ($p= 0.04$). Finally, mEH gene polymorphisms was found to be associated also with OVS and DFS.

Overall, the study design was sound. However, several concerns need to be addressed before publication.

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

1. Abstract: the Authors should emphasize that the association they found between mEH and OVS and DFS is true only in the subset of selected patients axillary lymph node negative/positive.

2. Subjects paragraph: the Authors should describe how they matched the controls to the cases.

3. Polymorphism analysis paragraph: the Authors should state the kind of laboratory controls they used to perform the analysis, i.e. if they were unaware of the status of samples, if they run blinded duplicates, if they use positive and negative controls during the experiments.

4. Result line 6-7: the Authors stressed that the CYP2D6 G/G genotype was associated with the late onset of breast cancer, but they should state also that the heterozygous state seems to be protective (Confidence Intervals are missing)
5. Results line 11-16: the Authors state that individuals with at least one copy of CYP2D6 mutant allele have reduced risk of breast cancer, but their results show the contrary at least in postmenopausal women. Please clarify this issue.

6. Table 1: the title is not correct; the table illustrates the primers and restriction enzymes used for all the XME polymorphisms investigated.

7. Table 2: there are some genotypes missing; it should be stated in the result paragraph and if possible added into the table.

8. Table 2 and 3: the Authors should add the 95% CI for all the ORs calculated.

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

1. Subjects paragraph: “…subjects selected form the SAME population…”. It is not clear the term “same”. Please specify.

2. Subjects paragraph: “control subjects’ mean age…”. There is a typo. A ± symbol should be used.

3. Statistical analysis paragraph: please type in capital letters “Hardy-Weinberg”

4. Results paragraph: the genotype distributions did not diverge significantly from H-W equilibrium: is it true also for the control group alone?

5. Results line 3: I guess the word “when” is missing before the sentence “the patients were stratified according to their menopausal status…”.

6. Discussion line 2: please add the word “patients” after “postmenopausal”.

7. Discussion NAT2 part: the association between NAT2 slow acetylator and breast cancer has not been seen in other studies means that the Authors’ results are discordant with previous papers? Please clarify the meaning.

8. Discussion line 9 and 15 from the end: “mEH wild genotype” should be changed into “mEH wild-type genotype”

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Discretionary Revisions (which the author can choose to ignore)

1. Results line 12: “but” should be corrected with “while”

2. Results line 13: “of” should be corrected with “among the”

3. Results line 14: “a risk factor to” should be corrected with “a risk factor for”

4. Even if the population has been described elsewhere, I guess a descriptive table, containing also the information on axillary lymph node status, could be useful.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
**Level of interest:** An article of importance in its field

**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