Author's response to reviews

Title: Correlation of breast cancer risk factors with HER-2/neu protein overexpression according to menopausal and estrogen receptor status.

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Author's response to reviews: see over
Dear Editors:

Thank you for the reviewers’ comments on the manuscript entitled: “Correlation of breast cancer risk factors with HER-2/neu protein overexpression according to menopausal and estrogen receptor status”. We now submit a revised version of the manuscript on the basis of the comments and suggestions. We have also had the English in the manuscript checked and corrected by a native speaker.

Below we present a point-by-point response to the comments.

Major revisions:

1. We agree concerning the reliability of age-adjusted estimates in table 3 and this table has been omitted from the revised manuscript. Instead, we have added a new column to table 1 with the significant multivariate case-control OR’s adjusted for confounding factors. We present only the significant (or markedly significant) OR’s, which are the only estimates that could be derived by this type of regression (backward and stepwise). We hope that the table is not now too busy and confusing. We also revised text in the Results section (concerning points 1 and 2).

2. We agree about the interpretation of the case to case OR’s. The relevant paragraphs (in Results and Discussion sections) have been revised according to your reviewer’s comments (pages 12-17).

3. There was a typing error concerning the study period, for which we must apologise. The study concerns the time period from 1996 to 2002. Every woman attending our Breast Unit who was newly diagnosed with invasive breast cancer during that time period has been included in the present study, except for those who met the exclusion criteria described in the Methods section. This is now clearly stated on page 8: (“The study considered all women who were consecutively diagnosed with primary, invasive breast cancer in our unit from 1996 to 2002. Subjects of other races, ethnicity, with residence outside Crete or diagnosed with DCIS or LCIS were excluded. Finally, 384 women, all originating from the island of Crete, were eligible for analysis.”) The breast cancer patients who participated in this
study constitute a rather representative sample of the female population of the island of Crete, since they originated from all rural and urban areas of the island (data not shown), with no significant differences in any other characteristics (e.g. family history, etc).

**Minor revisions:**

4. We have revised the sentence as follows: “As a result, some researchers have maintained that HER-2/neu amplification and/or protein overexpression may also represent not only an important marker of prognosis but also a key indicator of the aetiological heterogeneity of breast carcinogenesis.” Page 6.

5. The cut-off point for BMI represents the median value of both cases and controls (in fact it was 28.95 kg/m²). The time period threshold for OC and HRT use was 2 months and we have clarified this in the Methods section, page 9.

6. We have added a new paragraph concerning the retrieval rate, page 9, as well as a comment in table 2: “For this study, tumour blocks were successfully retrieved in 378 (98.4%) and in 377 (98.17%) of the 384 interviewed cases for the immunohistochemical detection of HER-2/neu protein and hormone-receptor expression, respectively”.

7. Each subject, with or without malignancy, who participated in this study followed the same standard procedure as regards the Breast Unit’s routine screening programme. For this reason we can see no reason for any differences in recall between cases and controls, except for those related to each individual, such as memory and other strictly personal characteristics. The interview was carefully conducted for every woman who participated in this study, prior to any diagnosis or other intervention, and we consider that the value of the information collected is the best possible for this kind of research.

In making this revised submission we appreciate the commentary, which has indeed resulted in a finer and more detailed manuscript. We hope that this manuscript is now in a form acceptable for publication in the *BMC Women's Health*.

_Sincerely yours._

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