Author's response to reviews

Title: Favourable Ten-Year Overall Survival in a Caucasian Population with High Probability of Hereditary Breast Cancer

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Version: 5 Date: 10 February 2010

Dear Editor,

here enclosed you can find the final revision aimed to improve the English language provided by a commercial copyediting service. We have paid particular attention to the abstract session, as you have recommended.

The abstract has been changed in the Conclusions session as following:

....prognosis than those (eliminated "the") with sporadic BC. Considering these results, women who previously had BC (eliminated "affected by") and had survived (added) ten years could be selected for BRCA1 analysis among family members (eliminated "members of") at high risk of hereditary BC during genetic counselling (shifted from the beginning of the phrase). Since only 30% of patients with a high probability of having (eliminated "being") hereditary BC have (eliminated "results in a")BRCA1 mutations, selecting women with a long term survival (eliminated "OS")among this population could increase the rate of positive analyses (modified), avoiding the use (eliminted"useless") of expensive tests.

Statistical analysis session in "Patients and Methods":

....matches were (eliminated "matching was")assigned between BRCA1 and patients with sporadic BC (added) of the same age at diagnosis (range, between 26 and 76 +/- 4 years), tumour grade (added) (I, II, and III), and stage (I, II, and III). Multivariate analyses of DFS and OS were conducted using a proportional hazards Cox regression model. All statistical analyses were done (eliminted "carried out") with SPSS, version 12.0 (SPSS Inc, Chicago, IL).

Results (Patients Characteristics):

The (added) patients’ characteristics are detailed in Table 1. The H risk group
presented with a medullary carcinoma histotype more frequently than the other two groups (p<.0001). The H risk group was more likely to have stage II disease than the sporadic and IS increased risk groups (p<.0001), and to have a significantly lower estrogen receptor (ER) and progesterone receptor (PgR) expression levels (shifted from lower "levels of") (p<.0001) as measured by immunohistochemical analysis (clone 6F11, Ventana, for ER; and clone 1E2, Ventana, for PgR) and stained by Ventana Benchmark autostainer.

Survival analysis session:

The study group of 80 BRCA1 cases was compared with 320 matched sporadic cases from the Modena cancer registry who were (eliminated "with") the same age, and had the same (added) tumour grade (eliminated "grading") and stage. Results are shown in Fig. 2. A statistically significant difference in OS was seen for BRCA1 patients compared (eliminated "in comparison") with sporadic BC (85% vs. 73%, respectively, p=.05).

Discussion chapter:

...carriers had a better OS than patients considered at IS increased (eliminated "probability") risk or to have sporadic breast

....Furthermore, BRCA1 carriers may (eliminated "could") be more likely to be found among (eliminated "selecting") women who have (eliminated "with a") a high probability of hereditary breast cancer (eliminated "among patients with a high probability of being hereditary") and who have a long term survival (eliminated "OS"). If BRCA1 carriers could be identified through these characteristics, the use of expensive tests could be avoided (eliminated "avoiding useless") and the rate of positive (eliminated "positive rate") analyses increased (eliminated "increasing").

Our study involves a very large number of Caucasian patients with (eliminated "affected by") breast cancer (N=5923) who were first evaluated for their family history of breast cancer and subsequently for BRCA1 status. The most common weakness of previous studies includes (added) the small number of patients or selection bias, such as a retrospective analysis for (eliminated "the") BRCA1 status.

...patients maintain a statistically significant OS advantage (changed), even after (eliminated "having") matching each case to four controls for age and tumour (added) grade and disease stage, this result is very important in terms of its (added, eliminated "of") practical value, because all confounders have been removed.

...Hence (eliminated "so"), increasing (eliminated "the") the number of BRCA1 carriers identified by (eliminated "performing a") correctly selecting patients with a (eliminated "at") high probability of having (added) hereditary breast cancer through a 10-year survival (added) analysis could improve the benefit derived from specific chemotherapy agents (shifted) (i.e., (added) alkylating or PARP-inhibitors).

Figure legend 2:

Fig. 2 - Probability of survival in 80 BRCA1 breast cancer cases and 320
sporadic breast cancer controls matched for age and tumour grade (added) and stage, using Kaplan–Meier analysis. There was a statistically significant difference between the two groups (log-rank test, p=.05).

We hope that revision will render the manuscript acceptable for publication in your journal.

Sincerely,

Laura Cortesi