**LETTER TO JMG**

A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer

P O Chappuis, J Goffin, N Wong, C Perret, P Ghadirian, P N Tonin, W D Foulkes

**MATERIAL AND METHODS**

To address the question of initial response to chemotherapy for hereditary breast cancer, we reviewed all cases of Ashkenazi Jewish (AJ) or French Canadian (FC) women treated with neoadjuvant chemotherapy and for whom founder BRCA1/2 mutation status had been determined through genetic testing facilities in Montreal, QC. We have a clinicopathological database of 615 AJ or FC women who have been tested for the known founder mutations in BRCA1/2 that are present in these two populations. This testing was performed in both clinical and research settings between 1995 and 2001. By comparing this database with one containing women treated by neoadjuvant chemotherapy at McGill University or Université de Montréal hospitals, we identified 38 women (seven BRCA1 mutation carriers (hereafter “carriers”), four BRCA2 carriers, and 27 non-carriers) who developed histologically or cytologically diagnosed primary breast cancer (stages I-III) and received neoadjuvant treatment. Not carrying a germline BRCA1/2 mutation was defined as follows: (1) for Ashkenazi Jewish patients (n=12), absence of the three BRCA1/2 founder mutations; and (2) for patients of French Canadian origin (n=15), absence of seven BRCA1/2 founder mutations as well as a BRCAPRO score of <2%. One woman (J007) was identified as a BRCA1 carrier 13 months before developing breast cancer and another (AJ32) was identified as a BRCA1/2 non-carrier 17 months before her diagnosis. In all other cases, genetic testing was performed at or after breast cancer diagnosis. The period of time that elapsed between breast cancer diagnosis and genetic testing was not statistically different among BRCA1/2 carriers and non-carriers (median 0.5 year < 0.3 year, respectively, p=0.84, Mann-Whitney U test).

The full clinicopathological details of the 38 subjects are shown in supplementary tables 1 and 2 (www.jmedgenet.com). Twenty-six out of 38 patients (6/11 carriers and 20/27 non-carriers, p=0.28) were included in prospective multicentre clinical trials that evaluated neoadjuvant treatment in breast cancer (NSABP-B18, -B26, and -B27, NCIC MA.10). Except for one patient (AJ32) treated with paclitaxel alone, all patients received anthracyclin based chemotherapy (usually four cycles) before surgery. After neoadjuvant treatment, all except two patients (1236 and 98120) underwent either a lumpectomy or segmental mastectomy with axillary lymph node dissection or a modified radical mastectomy. Clinical response was defined as: (1) complete response (CR), no residual palpable disease; (2) partial response (PR), ≥50% reduction in bidimensional measurements of the breast mass and axillary adenopathy; (3) no change, between 50% reduction and 25% increase in tumour size; or (4) progressive disease, >25% increase in tumour size. As various regimens of neoadjuvant chemotherapy were administered, clinical response was systematically evaluated after three or four cycles of chemotherapy, and further clinical responses after any subsequent cycles were not included in any of our analyses (for full details, see supplementary tables 1 and 2). Pathological complete response (pCR) was recorded when there was no evidence of residual tumour cells in the breast and axillary lymph nodes. For the other cases, the pathological response was considered incomplete. No patient showed residual non-invasive (in situ) tumour cells without invasive component.

**RESULTS**

No significant difference was noted between carriers and non-carriers for age at diagnosis (mean (median) 44.1, SD 8.4 (43.4) years v 47.6, SD 11.4 (46.2) years, p=0.37), tumour size (mean (median) 5.5, SD 2.6 (6.0) cm v 4.9, SD 3.0 (4.0) cm.

**Abbreviations:** AJ, Ashkenazi Jewish; FC, French Canadian; cCR, clinical complete response; pCR, pathological complete response; CR, complete response; PR, partial response; ER, oestrogen receptor

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response rates in carriers.

women were testing could be offered. If a substantial proportion of such who received neoadjuvant chemotherapy, but died before cohort study, we did not have the opportunity to study women carriers and non-carriers. As this is not a prospective (incident)

to neoadjuvant treatment observed in (supplementary tables 1 and 2). After three or four cycles of neoadjuvant chemotherapy, a cCR was recorded in 10 of 11 BRCA1/2 carriers (93%) compared with eight of 27 non-carriers (30%), \( p=0.0009 \) (table 1A). Notably, four (two BRCA1 carriers and two BRCA2 carriers) of nine (44%) evaluable BRCA1/2 carriers had no residual tumour in the breast and the axillary lymph nodes (pCR), whereas only one case of pCR (4%) was noted among the non-carriers (\( p=0.009 \), table 1B). When we matched the cases 1:1 to controls on precise TNM stage, the significance of the effect of mutation status on complete clinical response rate was slightly less marked (table 1A), reflecting the smaller sample size. Similarly, when we analysed pCR in the matched series of 18 carriers and non-carriers, the effect diminished and is of borderline statistical significance (table 1B).

DISCUSSION

We report here preliminary evidence for a differential response to neoadjuvant chemotherapy for breast cancer on the basis of germline BRCA1/2 mutation status. BRCA1/2 carriers showed a better clinical response rate to neoadjuvant chemotherapy than did non-carriers. Importantly, the clinical and pathological responses to neoadjuvant treatment observed in BRCA1/2 non-carriers were concordant with what has been reported previously. The probability of a CR appears to be independent of clinical stage\(^6\) and here we found that the four pCRs seen among the carriers were distributed in all initial stages (supplementary table 1).

We recognise that this study has several limitations. In particular, this is a very small series of patients who were identified through established research and clinical protocols for BRCA1/2 mutation analysis, and the criteria for testing differed from study to study and over time. As such, and because of a clinic based selection, there is a possibility of bias. The most important bias would be a survival bias, but we have shown that this can be excluded, as there were no important differences in the time intervals between breast cancer diagnosis and BRCA1/2 mutation testing when comparing carriers and non-carriers. As this is not a prospective (incident) cohort study, we did not have the opportunity to study women who received neoadjuvant chemotherapy, but died before testing could be offered. If a substantial proportion of such women were BRCA1/2 carriers, we may have overestimated the response rates in carriers.

One might expect that the breast cancers occurring in our series of carriers would have different clinicopathological features than those seen in non-carriers, as these differences are well known.\(^7\) In the unmatched analyses, we did not observe significant differences for age at diagnosis, ER status, or tumour grade among carriers and non-carriers, although some non-significant differences were noted. It is possible that the small sample size and the younger than expected age of the controls accounts for this finding. Whatever the reason for the lack of difference, the clinicopathological characteristics of the breast cancers occurring in carriers and non-carriers, whether matched or unmatched, suggests that such potential differences are unlikely to explain the results we observed, particularly as a statistically significant difference in clinical response rates was observed when close matching was performed.

Another possibility is that pCR was preferentially achieved by carriers because they received more chemotherapy before pathological confirmation of response. However, only one carrier with pCR received more than four cycles of neoadjuvant chemotherapy, and this woman (J322, supplementary table 1) had achieved a cCR after four cycles of doxorubicin and cyclophosphamide. Moreover, five non-carriers (supplementary table 2) received more than four cycles of neoadjuvant chemotherapy without achieving a pCR, so it does not appear that adding further chemotherapy after the fourth cycle is the reason why, overall, carriers were statistically significantly more likely to achieve pCR than were non-carriers.

As stated above, the breast cancers occurring in BRCA1/2 carriers and non-carriers did not significantly differ in terms of standard clinicopathological variables. It is therefore tempting to speculate that it is the presence of the germline BRCA1/2 mutation per se that is determining the difference in response to neoadjuvant chemotherapy.

Considering outcome, women who have a cCR and/or pCR have a better long term outcome than women who do not achieve a CR.\(^6\) Presumably, those who achieve CR are more likely to have eliminated micrometastases. We and others previously showed that BRCA1/2 mutation status is associated with a worse outcome after invasive breast cancer.\(^\text{17-22}\) This apparent paradox of a very good initial response to preoperative chemotherapy among carriers and a worse long term survival needs further study. Of note, no survival studies have been stratified according to the administration of adjuvant chemotherapy. Among a cohort of 292 Ashkenazi Jewish women diagnosed with invasive breast cancer between 1980 and 1995, we recently showed that the overall survival was significantly worse among BRCA1 mutation carriers compared to non-carriers, but only among patients who did not receive adjuvant chemotherapy.\(^\text{23}\) Putting our two observations together, one might speculate that the poor survival observed in some retrospective series is partly explained by the omission of chemotherapy in these historical series, and that

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**Table 1** (A) Clinical and (B) pathological responses to neoadjuvant chemotherapy in BRCA1/2 carriers and non-carriers

<table>
<thead>
<tr>
<th>A</th>
<th>Clinical complete response</th>
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<td>1</td>
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<tr>
<td>Non-carriers</td>
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<table>
<thead>
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<th>Pathological complete response</th>
<th>Less than pathological complete response</th>
<th>p value</th>
</tr>
</thead>
<tbody>
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<td>5</td>
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<tr>
<td>Non-carriers</td>
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<tr>
<td>Matched*</td>
<td>0</td>
<td>9</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Carriers were matched to controls on TNM stage and on closest age (means 44.1 and 44.3 years, \( p=0.95 \)) and grade.
†Two carriers who had a clinical complete response were excluded from this analysis because they did not have any further surgery after neoadjuvant chemotherapy.
this might have been ameliorated by adjuvant chemotherapy. Therefore, as little is known about the in vivo response of BRCA1/2 related breast cancer to chemotherapy agents, it will be important to establish whether the very promising initial response to neoadjuvant chemotherapy we observed in BRCA1/2 carriers will be sustained. Larger, prospective studies will be required to confirm or refute our preliminary observations.

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REFERENCES


Supplementary tables 1 and 2 can be found on the journal website at www.jmg.bmj.com.
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