LETTER TO JMG

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

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Neoadjuvant (preoperative) chemotherapy was initially developed as a first line treatment for locally advanced breast cancer. More recently, it has been used to treat earlier stage operable disease, with the hope that not only could the treatment be used as an in vivo assessment of tumour response, but also that it might more readily eradicate occult distant micrometastases. Many studies have shown a small but significant increase in breast conservation when neoadjuvant chemotherapy was used but, overall, most randomised studies have not shown any survival advantage following this treatment.[1 2] Despite this, it has been noted that women receiving neoadjuvant chemotherapy who experience either a clinical complete response (cCR) (≤40% of all those treated) or, more clearly, a pathological complete response (pCR) (≤10%) have a better long term outcome than women who achieve less than a complete response.[1 2]

Germline mutations in the *BRCA1* and *BRCA2* genes are the major genetic predisposition to breast cancer. Some of the functions of BRCA1 and BRCA2 proteins could be directly involved in response to cytotoxic agents, such as the role of BRCA1/2 in DNA repair[3] or apoptosis.[4 5] Distinct pathological features[6] and gene expression profiles[7] suggest that there are differences in hereditary breast cancer compared to sporadic cases, which might lead to differences in treatment response. In vitro data suggest that cells without functional BRCA1 or BRCA2 protein are particularly sensitive to several chemotherapeutic drugs[4] or ionising radiation.[8] Mouse and human cell lines deficient in BRCA1 or BRCA2 display an increased sensitivity to agents causing double strand DNA breaks.[9 10] This hypersensitivity has been shown for mitoxantrone, amsacrine, etoposide, doxorubicin, and cisplatin with a subsequent increased level of apoptosis.[9 11–13] Differences in drug sensitivity might be explained by interaction of BRCA1/2 proteins with various pathways leading to apoptosis.[13 14] These findings raise the question of the efficacy of adjuvant chemo- or hormonotherapy for breast cancer among women who carry a germline *BRCA1/2* mutation.

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.[15 16] 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[15]; and (2) for patients of French Canadian origin (n=15), absence of seven *BRCA1/2* founder mutations[16] 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 *v* 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

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

A	Clinical complete response	Less than clinical complete response	p value
BRCA1/2 carriers	10	1	–
Non-carriers			
Unmatched	8	19	0.0009
Matched*	2	9	0.002
B	**Pathological complete response**	**Less than pathological complete response**	**p value**
BRCA1/2 carriers†	4	5	–
Non-carriers			
Unmatched	1	26	0.009
Matched*	0	9	0.08

*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.

p=0.52), oestrogen receptor (ER) status (p=0.23), or tumour grade (mean (median) 2.6, SD 0.50 (3) *v* 2.4, SD 0.76 (3), p=0.44) (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.[1] The probability of a CR appears to be independent of clinical stage[17 18] 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.[6] 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.[2 17 19 20] 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.[21–23] 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.[24] 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

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

Supplementary Table 1 Breast cancer patients carrying a *BRCA1/2* germline mutation and treated with neoadjuvant chemotherapy: clinicopathological characteristics and response to treatment

ID	Age at diagnosis	Mutation type	Amino acid change	cT (cm)	cN	Histological type	Grade	ER status	Neoadjuvant chemotherapy	Tamoxifen*	Clinical response	Pathological response
AJ257	60.4	*BRCA2*: 6174delT	Stop 2003	8.0	1	Ductal	3	Neg	FACx3	No	Complete	Complete
J279	47.6	*BRCA1*: 4446C>T	R1443X	7.0	0	Undifferentiated	3	Neg	ACx4	Yes	Complete	Complete
J322	47.5	*BRCA2*: 8765delAG	Stop 2867	1.3	0	Ductal	2	Pos	ACx4 + Dx4	Yes	Complete†	Complete
1162	31.9	*BRCA1*: 4446C>T	R1443X	4.2	0	Undifferentiated	3	NA	ACx4	Yes	Complete	Complete
J007	43.4	*BRCA1*: 5382insC	Stop 1829	10.0	1	Ductal	3	Pos	ACx4	Yes	Complete	Incomplete
J415	50.6	*BRCA2*: 6174delT	Stop 2003	6.0	1	Ductal	3‡	Pos‡	ACx4	No	Complete	Incomplete
1108	32.2	*BRCA2*: 6085G>T	E1953X	7.0	1	Ductal	2	Neg‡	CEFx3	NA	Complete	Incomplete
99076	38.9	*BRCA1*: 185delAG	Stop 39	6.3	1	Ductal	3‡	Neg‡	FACx4	No	Complete	Incomplete
1236	49.9	*BRCA1*: 4446C>T	R1443X	6.0	0	Adenoca	2	NA	ACx4 + CMFx6	Yes	Complete‡	NE
98120	40.3	*BRCA1*: 4446C>T	R1443X	2.0	0	Ductal	3	Neg	FACx4	No	Complete	NE
1134	42.2	*BRCA1*: 4446C>T	R1443X	3.0	1	Ductal	2	Neg‡	ACx4 + Dx4	Yes	Partial‡	Incomplete

A, doxorubicin (Adriamycin®); adenoca, adenocarcinoma; C, cyclophophamide; cN, clinical axillary lymph node status; cT, clinical tumour size; D, docetaxel (Taxotere®); E, epirubicin; ER, oestrogen receptor; F, 5-fluorouracil; M, methotrexate; NA, not available; NE, not evaluable; Neg, negative; Pos, positive.

*Concomitant administration with the neoadjuvant chemotherapy.

†Evaluated after four cycles of chemotherapy.

‡Evaluated after the neoadjuvant chemotherapy (at the time of surgery).

Supplementary Table 2 Breast cancer patients who do not carry a *BRCA1/2* germline mutation, treated with neoadjuvant chemotherapy: clinico-pathological characteristics and response to treatment

ID	Age at diagnosis	cT (cm)	cN	Histological type	Grade	ER status	Neoadjuvant chemotherapy	Tamoxifen*	Clinical response	Pathological response
1279	36.7	2.5	1	Ductal	3	Neg	ACx4	Yes	Complete	Complete
1191	39.3	8.0	1	Ductal	2‡	NA	ACx4	No	Complete	Incomplete
AJ59	47.5	10.0	0	Ductal	3	Pos	ECx6	No	Complete†	Incomplete
AJ79	60.8	1.0	0	Ductal	1‡	Pos‡	ACx4	No	Complete	Incomplete
AJ115	50.4	3.5	0	Adenoca	3‡	Neg‡	ACx4	No	Complete	Incomplete
AJ279	52.8	2.0	0	Ductal	2‡	Neg‡	ACx4	No	Complete	Incomplete
FC117	54.6	3.2	0	Ductal	3	Pos	ACx4	Yes	Complete	Incomplete
1250	40.0	2.0	0	Ductal	NA	Pos	ACx4	Yes	Complete	Incomplete
AJ396	58.2	10.0	0	Ductal	3	Neg	FACx6	No	Partial†	Incomplete
AJ32	46.2	11.0	0	Ductal	3‡	Neg‡	Px4	No	Partial	Incomplete
AJ84	54.8	5.0	1	Ductal	3	Neg‡	ACx4	No	Partial	Incomplete
AJ142	44.8	2.0	0	Ductal	3‡	Pos‡	ACx4	No	Partial	Incomplete
FC59	58.0	5.0	0	Ductal	2‡	Pos‡	ACx4	Yes	Partial	Incomplete
FC80	48.0	4.0	0	Ductal	1‡	Pos‡	ACx4	Yes	Partial	Incomplete
J418	38.2	2.5	0	Ductal	2	NA	ACx4	No	Partial	Incomplete
1129	34.8	6.0	1	Ductal	2	Pos‡	ACx4	No	Partial	Incomplete
1138	39.2	3.4	1	Ductal	1	Pos‡	ACx4	Yes	Partial	Incomplete
1139	35.3	3.0	0	Ductal	3	Pos‡	ACx4	Yes	Partial	Incomplete
1179	34.3	2.8	0	Ductal	2‡	Pos‡	ACx4	Yes	Partial	Incomplete
1209	35.9	6.0	0	Ductal	3	Neg	ACx4 + Dx4	Yes	Partial†	Incomplete
1218	39.9	3.0	0	Ductal	3‡	Pos	ACx4	Yes	Partial	Incomplete
1238	39.7	4.0	1	Ductal	3	Pos	ACx4	No	Partial	Incomplete
1249	38.9	2.6	0	Ductal	1	Pos	ACx4	Yes	Partial	Incomplete
98114	70.1	4.5	0	Ductal	NA	Pos‡	ACx4	Yes	Partial	Incomplete
AJ156	48.7	7.0	0	Ductal	3‡	Pos‡	ACx5	No	Partial†	Incomplete
AJ386	57.7	12.0	1	Ductal	3‡	Neg	FACx6	No	No change†	Incomplete
97008	79.4	5.0	0	Ductal	3‡	Neg‡	ACx4	No	No change	Incomplete

A, doxorubicin (Adriamycin®); adenoca, adenocarcinoma; C, cyclophophamide; cN, clinical axillary lymph node status; cT, clinical tumour size; D, docetaxel (Taxotere®); E, epirubicin; ER, oestrogen receptor; F, 5-fluorouracil; NA, not available; Neg, negative; P, paclitaxel (Taxol®); Pos, positive.

*Concomitant administration with the neoadjuvant chemotherapy.

†Evaluated after four cycles of chemotherapy.

‡Evaluated after the neoadjuvant chemotherapy (at the time of surgery).