Editorial

Outcomes in *BRCA* mutation carriers: evaluation of current data for optimal clinical care

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BRCA1 and *BRCA2* are genes responsible for homologous recombination and repair of double-strand DNA breaks (1). Mutations in either gene increase the risk of malignancy and are responsible for the hereditary breast and ovarian cancer syndrome (HBOC). The lifetime incidence of breast cancer in those harboring *BRCA1* or *BRCA2* mutations has been estimated to be greater than 80% (2,3). The biology of *BRCA1/2* mutation associated cancers is unique. *BRCA1* mutated tumors in particular are often estrogen receptor (ER) and HER2 negative and express a phenotype of a basal-type breast cancer (4). They are typically higher-grade tumors, with more metastatic potential and poorer outcomes (5). There has also been interest in the potential susceptibility of BRCA-mutated cancers to therapeutic agents, such as platinum-derived chemotherapy and PARP inhibitors, that take advantage of the defect in homologous DNA repair, so-called "synthetic lethality" (6).

Despite an understanding of the incidence and biology of these *BRCA*-associated cancers, there has been no clear evidence on the impact of these mutations on breast cancer-specific survival compared to non-carriers. Prior studies have been conflicting and plagued by small numbers, selection, and survivor bias (7,8). The latter is often secondary to including women who were able to agree to blood-based genetic testing selected for those who did not suffer from early recurrence and mortality. Retrospective tissue based testing has been seen as a way to avoid this pitfall, but small numbers and methodology often not accounting for risk-reducing intervention have prevented clear insight.

In their publication in the *Journal of the National Cancer Institute*, Schmidt, van den Broek *et al.* analyzed a cohort of 6,478 women younger than 50 years of age with breast cancer to assess long-term survival differences between *BRCA1/2* mutation carriers and non-carriers (9). This was an unselected cohort of women from ten Dutch hospitals. To avoid survivor bias, the investigators determined germline *BRCA1/2* mutation status using formalin-fixed paraffin-embedded non-tumor tissue for most patients. After excluding those with synchronous bilateral cancers, metastatic disease at or within 3 months of diagnosis, and without adequate DNA for analysis; 6,304 patients were suitable for overall survival (OS) analysis. Fewer patients had sufficient clinical data for assessment of breast cancer-specific survival and disease and metastasis-free survival, 3,515 and 3,440 respectively. Median follow-up was an impressive 14 years. *BRCA1* and *BRCA2* mutation carriers made up 3.2% and 1.2% of the patients in this large cohort. The absolute difference in OS was about 10% for *BRCA1* (61.4%) *BRCA2* (60.95%) carriers compared to non-carriers (70.4%).

The 210 *BRCA1* carriers were more likely to develop ER-negative and triple-negative disease. In fact, 62.6% of *BRCA1* carriers had triple-negative disease as opposed to

Table 1 Overall survival events in *BRCA1* patients

BRCA1	HR for all follow-up	HR within 5 years of diagnosis
OS	1.28*	1.86*
Adjusted OS[#]	1.2	1.4
OS additionally adjusted for ovarian cancer**	1.1	–
BRCA1 carriers not receiving chemotherapy	1.54*	–

[#], hazard ratio adjusted for age at and calendar year of diagnosis, grade, size, nodal status, M-status, estrogen receptor status, chemotherapy, endocrine therapy, type of surgery (with and without radiotherapy), contralateral and ipsilateral breast mastectomy; *, P≤0.05; **, HR of *BRCA1* for overall survival before incidence of ovarian cancers.

Table 2 Overall survival events in *BRCA2* patients

BRCA2	HR for all follow-up	HR beyond 5 years of diagnosis
OS	1.26	1.56*
Adjusted OS[#]	1.06	1.47*

*, P≤0.05; [#], hazard ratio adjusted for age at and calendar year of diagnosis, grade, size, nodal status, M-status, estrogen receptor status, chemotherapy, endocrine therapy, type of surgery (with and without radiotherapy), contralateral and ipsilateral breast mastectomy.

only 18.3% of non-carriers. Perhaps unsurprisingly then, *BRCA1* carriers had a statistically significant worse OS with a hazard ratio (HR) for death of 1.28 (95% CI =1.05 to 1.57, P=0.01) compared to non-carriers, as described in *Table 1*. This difference appeared to be driven by mortality within the first 5 years of diagnosis, with a HR of 1.86 (95% CI =1.43 to 2.41, P≤0.001) during this period. OS variance was mitigated when adjusted for known prognostic indicators such as ER-receptor status, nodal status and treatment strategies; the adjusted HR being 1.2 (95% CI =0.97 to 1.47, P=0.09) for all follow-up and 1.4 (95% CI =1.07 to 1.84, P=0.02) for the first 5 years of follow-up. The investigators were unable to demonstrate a statistically significant change in breast cancer-specific survival in the adjusted group, even within the first 5 years of diagnosis. *BRCA1* was associated with increased risk of ovarian cancer, which was as expected a risk for death in *BRCA1* carriers and non-carriers. In fact, analysis of OS only including *BRCA1* patients prior to incidence of ovarian cancer largely negated the disparity in OS with a HR of 1.10 (95% CI =0.88 to 1.36, P=0.42). Taken together, this suggests the differential OS was driven largely by expected clinical characteristics such as more triple-negative disease and an increased risk of mortality from second ovarian cancers. Another notable finding is that not receiving adjuvant chemotherapy, even when adjusted for clinical and other treatment parameters, appeared to be a greater risk for mortality in *BRCA1* carriers compared to non-carriers. The adjusted HR was 1.54 (95% CI =1.08 to 2.19, P=0.02) in the *BRCA1* mutated group compared to control.

Analysis of *BRCA2* carriers is more limited given the small cohort of 75 patients. Results are summarized in *Table 2*. *BRCA2* carriers had a non-significant difference in OS regardless of clinical and pathologic factors with an unadjusted HR of 1.26 (95% CI =0.91 to 1.73, P=0.16) and adjusted HR of 1.06 (95% CI =0.77 to 1.47, P=0.71). They tended to be higher grade and involve lymph nodes. They had an inverted pattern of mortality compared to *BRCA1* carriers, with worse survival beyond 5 years of follow-up, as evidenced by a HR of 1.56 (95% CI =1.06 to 2.28, P=0.02). Adjusted for clinic-pathological factors, the HR for death after 5 years of follow-up was 1.47 (95% CI =1.00 to 2.17, P=0.05). The difference in OS including all years of follow-up was not statistically significant.

This retrospective analysis has a number of strengths. *BRCA1/2* testing was done on fixed non-tumor for the majority of patients. Moreover, 4,642 of 6,478 of the specimens were collected before 1995 meaning patients and clinicians were unlikely to be aware of *BRCA1/2* mutation status at time of treatment. However, the authors do note that many of these patients would go on to have eventual testing and likely increased screening, perhaps accounting for no difference in survival for those with second primary breast cancers. Results may have been diluted by the accidental inclusion of carriers in the inappropriate group as the authors state the *BRCA1/2* mutations tested account for about 61% of *BRCA1/2* mutations prevalent in the Netherlands. Another important observation was

the influence of secondary cancers on outcome, as many prior studies had failed to address the competing influence of ovarian cancer mortality. The overarching result that *BRCA*-related breast cancers have similar outcomes to other, sporadic cancers with similar clinical and pathologic features is compatible with results from analysis of an Israeli cohort. Rennert *et al.* investigated outcomes for women diagnosed with breast cancer from 1987 to 1988 in the Israel National Cancer Registry (10). They used fixed tissue for *BRCA1/2* testing and their cohort was not selected based on age or other clinical features. They found no difference in OS between carriers and non-carriers. However, they similarly observed earlier mortality among *BRCA1* carriers. Eighty-eight percent of deaths in *BRCA1* carriers occurred before 5 years of follow-up. *BRCA2* carriers had no statistically significant difference from non-carriers in terms of OS in either study. Limitations of this study include the majority of patients having unknown hormone receptor status. Schmidt and van den Broek *et al.* were able to obtain receptor status on all but 25.1% of patients. Their results are also compatible with their prior systematic review demonstrating only moderate evidence for a link to worsened OS in *BRCA* carriers when accounting for other risk factors (8).

As the authors have previously noted, the association with a lack of adjuvant therapy and worse survival in *BRCA1* patients is of interest. The results discussed here appear to confirm this concern. It may suggest a differential benefit to chemotherapy treatment in *BRCA1/2* carriers that normalizes risk in those treated with adjuvant chemotherapy. With the caveat that the study enrolled patients from 1970 to 2003, and few were likely to receive contemporary adjuvant chemotherapeutic regimens, the findings again raise the question of biological susceptibility enhancing the effect of chemotherapy in *BRCA1/2* deficiency. The pattern of worsened survival in the first 5 years after treatment of *BRCA1* carriers raises the question of earlier and more aggressive relapse in this group, even when accounting for traditional prognostic factors. The aforementioned Israeli registry study also demonstrated a statistically significant worse survival for *BRCA1* carriers who did not receive chemotherapy compared to non-carriers who did not receive chemotherapy with an adjusted HR of 1.59 (95% CI =1.01 to 2.50, P=0.04). This finding is also congruent with findings from a cohort of North American Ashkenazi Jewish women, also carried out retrospectively on fixed tissue to avoid selection bias, that showed *BRCA1* status predicted breast cancer mortality only among women who did not receive chemotherapy (HR 4.8, 95% CI: 2.0 to 11.7; P=0.001) (11).

Based on the studies presented to date it seems that *BRCA1/2* mutation carriers have similar survival patterns compared with non-carriers when controlling for type of cancer, treatment, age at diagnosis, and secondary ovarian cancers. *BRCA1* mutation carriers are more likely to develop TNBC and to have improved responses to chemotherapy (12,13). *BRCA1/2* mutation carriers with ER positive breast cancers have higher Oncotype Dx scores, providing again evidence of more aggressive disease amenable to chemotherapy (14). These findings help us clinically in focusing on prevention of breast cancer in *BRCA1/2* mutation carriers, aggressive treatment of *BRCA*-related breast cancer and prevention of subsequent malignancies such as ovarian cancer and contralateral breast cancer.

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