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Outcome of ovarian cancer after breast cancer in BRCA1 and BRCA2 mutation carriers

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Background: It is unknown whether a history of breast cancer (BC) affects the outcome of BRCA1/2-associated epithelial ovarian cancer (EOC). This was investigated in the current analysis.

Methods: We included 386 BRCA1/2-associated EOC patients diagnosed between 1980 and 2015. Progression-free survival (PFS), progression-free interval (PFI), overall survival (OS) and ovarian cancer-specific survival (OCSS) were compared between EOC patients with and without previous BC.

Results: BRCA-associated EOC patients with, vs without, a BC history had a significantly worse PFS and PFI (multivariate hazard ratio (HRmult) 1.47; 95% confidence interval (CI) 1.03–2.08 and HRmult 1.43; 95% CI 1.01–2.03), and a non-significantly worse OS (HRmult 1.15; 95% CI 0.84–1.57) and OCSS (HRmult 1.18; 95% CI 0.85–1.62). Ovarian cancer-specific survival was significantly worse for the subgroup treated with adjuvant chemotherapy for BC (HRmult 1.99; 95% CI 1.21–3.31).

Conclusions: Our results suggest that BRCA1/2-associated EOC patients with a previous BC have a worse outcome than EOC patients without BC, especially when treated with adjuvant chemotherapy.

It is assumed that 8–16% of all epithelial ovarian cancer (EOC) cases are due to BRCA1/2 germ line mutations (Risch et al, 2001; Thompson et al, 2002; Alsop et al, 2012). An improved survival after primary therapy has been reported for BRCA1/2-associated compared with sporadic EOC patients (Vencken et al, 2011; Yang et al, 2011; Hyman et al, 2012). This is thought to be explained by the crucial role of BRCA genes in homologous recombination, a mechanism to repair double-strand DNA breaks, which is deficient in patients without functional BRCA proteins. Platinum chemotherapy, like cisplatin or carboplatin, being a
cornerstone in EOC treatment, typically induces double-strand DNA breaks leading to more cancer cell death in BRCA1/2 mutation carriers.

Around 30–50% of the BRCA1/2-associated EOC patients have been treated for previous breast cancer (BC; Alsop et al, 2012; Vencken et al, 2013), whereas data on the incidence of EOC after

| Table 1. Patient, tumour and treatment characteristics of OC in BRCA1/2 patients with and without a history of BC |
|----------------------------------------------------------------------------------------------------------------|
| **Patients with a history of BC** | **%** | **Patients without a history of BC** | **%** | **P-value** |
| Total number of patients | 116 30 | 270 70 |  |  |
| Age at diagnosis |  |  |  |  |
| Median in years (range) | 53.1 (39.0–77.1) | 52.0 (23.2–89.7) | 0.09 |
| Mean in years (s.d.) | 54.3 (8.3) | 52.6 (9.1) |  |
| Follow-up time |  |  |  |  |
| Median in years (range) | 4.9 (0.4–33.4) | 5.6 (0.1–33.1) | 0.15 |
| Type of mutation |  |  |  |  |
| BRCA1 | 89 77 | 188 70 | 0.18 |
| BRCA2 | 27 23 | 82 30 |  |
| BRCA1/2 testing after EOC diagnosis* |  |  |  |  |
| Mean time after EOC in years | 3.6 | 4.3 | 82 | <0.001 |
| Median time after EOC in years | 1.4 | 2.2 |  |  |
| Year of diagnosis |  |  |  |  |
| 1980–1989 | 9 8 | 32 12 | 0.16 |
| 1990–1999 | 35 30 | 83 31 |  |
| 2000–2009 | 60 52 | 142 53 |  |
| ≥2010 | 12 10 | 13 5 |  |
| CA-125 (kU l−1) at primary diagnosis |  |  |  |  |
| <35 | 19 16 | 20 7 | 0.02 |
| 35–500 | 28 24 | 81 30 |  |
| >500 | 31 27 | 94 35 |  |
| Unknown | 38 33 | 75 28 |  |
| Histology |  |  |  |  |
| Serous | 75 65 | 166 62 | 0.77 |
| Mucinous | 5 4 | 8 3 |  |
| Endometrioid | 8 7 | 28 10 |  |
| Clear cell | 0 0 | 3 1 |  |
| Undifferentiated | 7 6 | 18 7 |  |
| Adenocarcinoma NOS | 16 14 | 34 13 |  |
| Other | 1 1 | 6 2 |  |
| Unknown | 4 3 | 7 3 |  |
| Tumour grade (Silverberg) |  |  |  |  |
| 1 (well differentiated) | 5 4 | 11 4 | 0.99 |
| 2 (moderately differentiated) | 24 21 | 55 20 |  |
| 3 (poorly differentiated) | 72 62 | 172 64 |  |
| Unknown | 15 13 | 32 12 |  |
| FIGO stage |  |  |  |  |
| I | 17 15 | 29 11 | 0.56 |
| II | 15 13 | 35 13 |  |
| III | 57 49 | 153 57 |  |
| IV | 23 20 | 48 18 |  |
| Unknown | 4 3 | 5 2 |  |
| Surgery |  |  |  |  |
| Primary surgery | 81 70 | 172 64 | 0.71 |
| Interval debulking | 9 8 | 24 9 |  |
| Both | 24 21 | 70 26 |  |
| None | 0 0 | 1 0 |  |
| Unknown | 2 2 | 3 1 |  |
| Radiotherapy |  |  |  |  |
| Yes | 5 4 | 10 4 | 0.79 |
| No | 103 89 | 236 87 |  |
| Unknown | 8 7 | 24 9 |  |
| Chemotherapy |  |  |  |  |
| Platinum with Paclitaxel | 77 66 | 182 67 | 0.68 |
| Platinum without Paclitaxel | 30 26 | 72 27 |  |
| Other | 3 3 | 2 1 |  |
| No | 6 5 | 11 4 |  |
| Unknown | 0 0 | 3 1 |  |
| Duration of chemotherapy for primary OC |  |  |  |  |
| Median in weeks (range) | 18.7 (1.3–47.7) | 20.0 (2.1–98.6) | 0.07 |
| Mean in weeks (s.d.) | 20.5 (7.9) | 22.7 (11.8) |  |

Abbreviations: BC – breast cancer; FIGO – international federation of gynecology and obstetrics; OC – ovarian cancer; NOS – not otherwise specified.

*Date of DNA test was missing for 18 patients (5 with and 13 without a BC history).
In the current study, we observed a significantly worse PFS and PFI, in BRCA-associated EOC patients with a BC history vs EOC patients without a previous BC, not yet resulting in a significantly worse survival. A significantly worse OCSS, however, was found in BC patients with and without a previous BC separately. To address the possible impact of adjuvant chemotherapy administered for BC on the PFS and OCSS of subsequent EOC patients with BC before OC treated with chemotherapy and patients not treated with adjuvant chemotherapy for BC were separately analysed and compared with EOC patients without previous BC (Figure 2 and Supplementary Table 3). We observed that PFS and OCSS were especially worse for patients treated with adjuvant chemotherapy for previous BC vs patients without previous BC (median 1.5 vs 2.0, and median 5.0 vs 5.3 years, respectively). In the multivariate analyses these differences were significant (HRmult 2.38; 95% CI 1.40–4.02 and HRmult 1.99; 95% CI 1.21–3.31, respectively). The patients with a BC history not treated with adjuvant chemotherapy had similar PFS and OCSS compared with EOC patients without a BC history (HRmult 1.16; 95% CI 0.76–1.79 and HRmult 0.87; 95% CI 0.59–1.29, respectively; Figure 2 and Supplementary Table 3).
No differences in grade, stage and histology were observed between both groups. A first hypothetical explanation for this survival difference might be that chemotherapy induces mutations and alters the behaviour of already present malignant EOC cells, or induces chromosomal instability in stem cells with subsequent development of EOC. Another possible explanation might be that treatment for the initial BC aggravates the (bone marrow) condition of the patient and, therefore, optimal therapy for EOC cannot be given to these patients. However, the time between BC diagnosis and OC diagnosis was not associated with outcome, suggesting that the condition of the patients is not the main reason for the worse survival in patients with a BC history.

The retrospective nature of the study brings corresponding limitations, such as different treatments regimens, and some missing data. Another limitation includes that the majority of the patients were tested for a BRCA1/2 mutation after EOC diagnosis (64% and 82% in the groups with and without a BC history, respectively), this will select for survivors. To account for this possible survivorship bias we have conducted left-truncation survival analyses. Because of the retrospective design, no firm conclusions can be drawn and our results should be confirmed in other (prospective) studies with greater sample size.

The results of this study underline the importance of offering genetic testing to BC patients being at risk of BRCA1/2 mutation carrierhip. Newly diagnosed mutation carriers can then be informed about risk reducing salpingo-oophorectomy, which has been associated with improved survival (Finch et al, 2014). Further,
we suggest that studies on survival in BRCA1/2-associated EOC should stratify for BC history.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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