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CLINICAL TRIAL

Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations

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Abstract More than 75% of breast cancers that develop in BRCA1 mutation carriers are triple-negative breast cancers (TNBC). The aim of this study was to compare the recurrence-free survival (RFS) and overall survival (OS) in high-risk patients with TNBC with and without deleterious BRCA1/2 mutations. A total of 227 women with TNBC who were referred for genetic counseling and underwent BRCA genetic testing between 1997 and 2010 were included in the study. The relationships between clinical variables and outcomes were evaluated using univariate and multivariate Cox proportional hazard regression models. Of 227 high-risk women with TNBC, 50% ($n = 114$) tested positive for BRCA1/2 mutations. Age, race, and tumor characteristics did not differ between BRCA non-carriers and carriers. At a median follow-up of 3.4 years, the 5-year RFS rates were 74 and 81% ($P = 0.21$), and 5-year OS rates were 85 and 93% in BRCA non-carriers and BRCA carriers, respectively ($P = 0.11$). In a multivariate model, after adjusting for age and disease stage, BRCA carriers tended to have a decreased risk of recurrence (HR = 0.67; 95% CI: 0.38–1.19; $P = 0.17$) or death (HR = 0.51; 95% CI:0.23–1.17; $P = 0.11$) compared to non-carriers. Our data indicate a 50% prevalence of deleterious BRCA1/2 mutations in high-risk women diagnosed with TNBC. Overall prognosis of TNBC in BRCA carriers and non-carriers is not significantly different within the first 5 years following an initial diagnosis. Further studies need to evaluate whether different therapies will change the outcome in these subgroups of TNBC.

Keywords Triple receptor-negative breast cancer · BRCA mutation · Survival · Recurrence · Chemotherapy

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Introduction

Triple-negative breast cancers (TNBC) are defined as tumors that lack expression of estrogen receptor (ER) and progesterone receptor (PR), but express human epidermal growth factor receptor-2 (HER2) at normal levels. TNBC affects 10–17% of all invasive breast cancers and is associated with poor prognosis. Microarray-based expression profiling studies have revealed five intrinsic subgroups of breast cancer, one of which is basal-like breast cancer [1]. This subgroup is characterized by an absence or low levels of expression of ER, an absence of HER2 overexpression, and expression of genes usually found in basal cells of the

normal breast [1, 2]. Although the majority of TNBC (approximately 80%) are also basal-like breast cancers, 18–40% of basal-like cancers do not have a triple-negative phenotype on immunohistochemical analysis (IHC) [3].

Immunohistochemical studies [4, 5] and expression arrays [6] have shown similarities between BRCA1 tumors and basal-like breast carcinomas. More than 75% of tumors arising in women carrying a BRCA1 mutation display a triple-negative phenotype, a basal-like phenotype, or both [2, 7]. Despite the higher prevalence of TNBC among BRCA mutation carriers, it is controversial whether BRCA carriers have lower survival, and previous studies have reported inconsistent results [8, 9]. With the presentation of the results of a recent large population study [10], it is an accepted general opinion that outcome for BRCA1/2 mutation carriers is at least as good as for non-carriers. Preclinical studies have suggested that lack of functioning BRCA1 or BRCA2 protein may result in differential treatment response to several agents targeting aberrant DNA repair pathways [11, 12]. Therefore, determining the prevalence of BRCA mutations in high-risk women with TNBC and survival outcomes in BRCA mutation-associated and non-BRCA mutation-associated TNBC is critical for the design of future clinical trials with novel therapeutics.

As a result, we conducted this retrospective analysis to determine whether there were any differences in the recurrence-free survival (RFS) and overall survival (OS) of patients with BRCA mutation-associated TNBC and non-BRCA mutation-associated TNBC.

Materials and methods

Patient population and data collection

The prospectively maintained Breast Cancer Management System database at the University of Texas MD Anderson Cancer Center (MDACC) identified 231 women with TNBC who were referred for genetic counseling and underwent genetic testing for mutations in the BRCA1 and BRCA2 genes between 1997 and 2010. All women were physician-referred to the Clinical Cancer Genetics Program at UTMDACC Breast Center based on family history (FH), and they were young aged ($\leq$50 years). Patients with bilateral disease, metastatic breast cancer, previous history of breast cancer (BC), or whose BRCA mutations indicated a variant of uncertain significance were excluded from the analysis.

This study was approved by the MDACC Institutional Review Board. The retrospective analysis of prospectively collected data included age at the time of diagnosis, FH of BC and/or ovarian cancer (OC), number of relatives affected with BC and/or OC, patient demographics, tumor characteristics, initial clinical stage, type of chemotherapy received, and surgery, recurrence and survival information.

Pathologic assessment and mutation analysis

All pathologic specimens were reviewed by dedicated breast pathologists at MDACC. Invasive carcinoma was confirmed on initial core biopsy specimens. Initial clinical stage and pathologic stage of all patients were revised and based on the sixth edition of the American Joint Committee on Cancer (AJCC) staging criteria [13]. Tumor grade was defined according to the modified Black's nuclear grading system [14]. Negative ER and PR status was defined as nuclear staining of $\leq$10% on IHC. HER2-negative status was defined as either $\leq$2+ or no staining by IHC and/or absence of gene amplification by fluorescence in situ hybridization.

BRCA testing was performed using germline DNA (from blood) by Myriad Genetics Laboratories Inc. (Salt Lake City, UT), and the test results were categorized as either positive or negative for a deleterious mutation.

Treatment

The types of chemotherapy received were at the discretion of the patient and multidisciplinary treating team. Neoadjuvant and adjuvant chemotherapy regimens comprised of anthracycline–taxane-containing regimens (AT) (n = 159); anthracycline-based regimens without a taxane (A) (n = 41); or single-agent taxane (T) (n = 5). Anthracycline-containing regimens included 3–6 cycles of one of the following: FEC100 (5-fluorouracil (5-FU) 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2); FEC75 (5-FU 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2); FAC (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2); or AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) intravenously (IV) on day 1 every 3 weeks. Taxanes co-administered with anthracyclines included paclitaxel 175–250 mg/m^2 or docetaxel 100 mg/m^2 IV on day 1 every 3 weeks for 4 cycles; or paclitaxel 80 mg/m^2 IV weekly for 12 doses. Patients who were treated with a taxane as a single agent received 4 cycles of docetaxel 60–100 mg/m^2 infused over 1 h or paclitaxel 225 mg/m^2 as a 24-hour infusion at 3-week intervals.

All patients underwent definitive surgery either before or after genetic testing. Contralateral prophylactic mastectomy (CPM) and bilateral prophylactic oophorectomy (BPO) were performed in women without evidence of metastatic disease. Postoperative radiotherapy was administered if patients had breast conserving surgery (BCS), locally advanced disease at presentation, primary tumor of

greater than 5 cm, or equal or greater than four involved axillary nodes. None of the patients received adjuvant endocrine therapy.

Statistical analysis and outcome measures

The demographic and clinical characteristics were summarized and compared between BRCA status group (non-carrier or carrier) by the chi-square test or Fisher's exact test. RFS was calculated from the time of surgery until the first date of documented disease recurrence or death or the date of last follow-up. OS was calculated from the time of surgery until the date of death from any cause or last follow-up. Patients not experiencing the relevant end points were censored at last follow-up. Survival outcomes were estimated using the Kaplan–Meier product-limit method and tested for differences between/among groups by log-rank test. Cox proportional hazards models were fitted to determine the association of BRCA status with time to event outcomes after adjustment for significant patient and clinical characteristics identified in univariate analyses. Of note, because of the high correlation between BRCA status and performance of BPO, to avoid colinearity, BPO was not included in the same multicovariate model. *P*-values ≤ 0.05 were considered statistically significant; all tests were two-sided. Statistical analysis was carried out using SAS 9.1.3 (SAS Institute Inc., Cary, NC) and S-Plus 8.0 (Insightful Corporation, Seattle, WA).

Results

Patient demographics and clinical characteristics

A total of 227 patients were identified for this analysis, of whom 50% ($n = 114$) were BRCA carriers, 82% ($n = 94$) were found to carry a BRCA1 mutation, and 19% ($n = 20$) were found to have a BRCA2 mutation. The prevalence of BRCA mutations with regard to patient demographics and clinical characteristics is displayed in Table 1. Age and menopausal status at diagnosis, race, nuclear grade, and initial clinical stage were not predictive of BRCA mutation status.

Nine patients had a previous history of OC, of whom eight had either BRCA1 ($n = 4$), or BRCA2 ($n = 4$) mutations, and one patient had both BRCA1 and two mutations**.** Among patients who did not report any FH of BC or OC ($n = 47$), the BRCA1/2 mutation prevalence was 23.4% ($n = 11$). Patients with a FH of BC or OC had a higher risk of having BRCA mutations compared to patients without any FH of BC or OC (57 vs. 29%; $P < 0.001$, and 77 vs. 41%; $P < 0.001$, respectively). Similarly, BRCA mutations were more frequently identified in patients with ≥ 2 family members with BC or OC compared to those with fewer relatives ($P < 0.001$).

Treatment effect

There were no significant differences in the use of chemotherapy regimen and type with respect to BRCA mutation status. Among the study population, the majority of patients (70%) received one of the anthracycline–taxane-containing regimens as neoadjuvant or adjuvant systemic therapy. Of 80 patients who were initially treated with neoadjuvant systemic chemotherapy (NST), 39% ($n = 31$) had stage III disease.

BCS was performed in 61% ($n = 49$) of patients in the BRCA non-carrier group vs. 39% ($n = 31$) in the BRCA carrier group ($P = 0.007$). Seventy-three percent of women (41/56) underwent BPO after genetic testing, and 59% ($n = 33$) of these women had a BPO within 1 year of receiving their test results. As expected, BPO was more frequently employed in BRCA carriers (91%) compared with BRCA non-carriers (9%) ($P < 0.001$). Likewise, 64% ($n = 55$) of carriers underwent a CPM while only 36% ($n = 31$) of non-carriers did ($P = 0.001$). However, this difference did not remain significant among patients ≤ 40 years of age. Among those patients, CPM was performed in 39% ($n = 22$) of carriers and in 25% ($n = 14$) of non-carriers ($P = 0.09$).

Survival estimates

Median follow-up of survivors was 3.4 years (range 0.02–21.0 years). A total of 25 deaths, and 51 recurrences or deaths were observed. The estimated 5-year RFS rates were 74% for BRCA non-carriers versus 81% for BRCA carriers ($P = 0.21$) (Fig. 1a). In univariate analyses, clinical stage III status and having received NST were factors associated with increased risk of breast cancer recurrence (Table 2). In contrast, older age (>40 years) and undergoing BPO were associated with a lower risk of recurrence. In the multivariate Cox proportional hazards model, patients with stage III disease had a higher risk of recurrence (HR = 3.81; 95% CI:1.58–9.20; $P = 0.003$), and older patients had a decreased risk of recurrence (HR = 0.39; 95% CI:0.21–0.71; $P = 0.002$). After adjusting for these significant clinical variables, BRCA status was not associated with RFS (HR = 0.67; 95% CI:0.38–1.19; $P = 0.17$).

The estimated 5-year OS rates were not significantly different among the two groups (85% in the BRCA non-carriers, and 93% in the BRCA carriers, $P = 0.11$) (Fig. 1b). In univariate analyses, clinical stage III status and treatment with NST were associated with increased risk for all-cause death, and older age and undergoing BPO

Table 1 Patient demographics and baseline clinical characteristics by BRCA groups

	BRCA non-carrier $N = 113$ (%)	BRCA carrier $N = 114$ (%)	P
Age			
Median (range)	40 (21–74)	41 (22–71)	
≤40	57 (50.9)	55 (49.1)	0.74
>40	56 (48.7)	59 (51.3)	
Race			
Black	11 (57.9)	8 (42.1)	0.76
White	82 (49.1)	85 (50.9)	
Others	20 (48.8)	21 (51.2)	
Premenopausal at diagnosis			
No	31 (54.4)	26 (45.6)	0.40
Yes	80 (47.9)	87 (52.1)	
FH of BC			
No	39 (70.9)	16 (29.1)	<0.001
Yes	74 (43)	98 (57)	
FH of OC			
No	99 (59.3)	68 (40.7)	<0.001
Yes	14 (23.3)	46 (76.7)	
Num rel with BC			
0	39 (70.9)	16 (29.1)	<0.001
1	28 (59.6)	19 (40.4)	
≥2	46 (36.8)	79 (63.2)	
Num rel with OC			
0	99 (59.3)	68 (40.7)	<0.001
1	13 (30.2)	30 (69.8)	
≥2	1 (5.9)	16 (94.1)	
Nuclear grade			
1–2	10 (62.5)	6 (37.5)	0.28
3	101 (48.6)	107 (51.4)	
Clinical stage			
I	26 (46.4)	30 (53.6)	0.88
II	62 (50.4)	61 (49.6)	
III	23 (50.0)	23 (50.0)	
Chemotherapy regimen			
AT	83 (52.2)	76 (47.8)	0.79
A	20 (48.8)	21 (51.2)	
T	2 (40)	3 (60)	
Chemotherapy type			
Adjuvant	58 (47.2)	65 (52.8)	0.43
Neoadjuvant	44 (55.7)	35 (44.3)	
Neither	4 (33.3)	8 (66.7)	
Both	5 (55.6)	4 (44.4)	
Surgery type			
Mastectomy	61 (42.4)	83 (57.6)	0.007
BCS	49 (61.3)	31 (38.8)	
Prophylactic mastectomy			
No	82 (58.2)	59 (41.8)	0.001
Yes	31 (36)	55 (64)	
Prophylactic oophorectomy			
No	94 (59.9)	63 (40.1)	<0.001
Yes	5 (9.3)	49 (90.7)	

FH family history, *BC* breast cancer, *OC* ovarian cancer, *Num rel with BC* number of relatives diagnosed with breast cancer, *Num rel with OC* number of relatives diagnosed with ovarian cancer, *AT* anthracycline–taxane-containing regimens, *A* anthracycline-based regimens without a taxane, *T* single-agent taxane, *BCS* breast conserving surgery

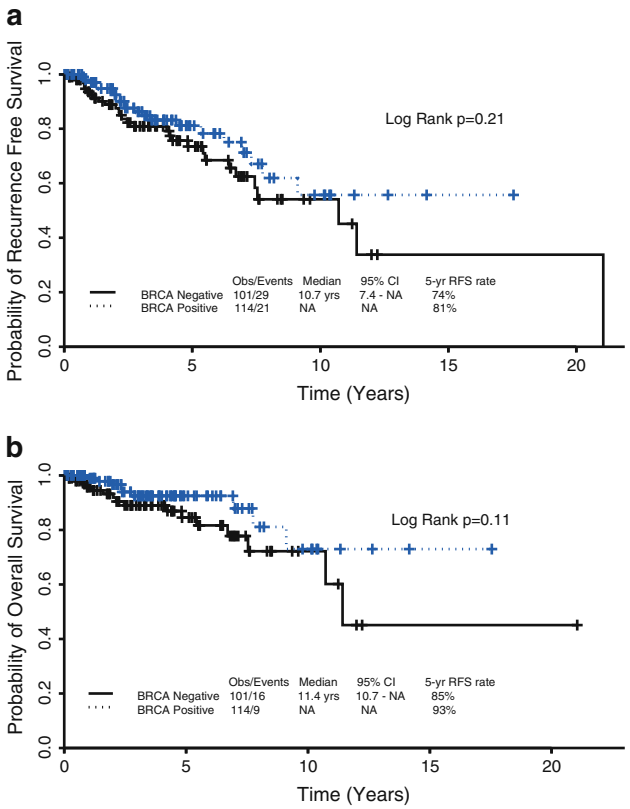

Fig. 1 Kaplan–Meier estimates of recurrence-free survival (RFS) (**a**) and overall survival (OS) (**b**) by BRCA status

were associated with a lower risk for death (Table 2). In multivariate analysis, while patients with stage III disease had a worse OS (HR = 3.39; 95% CI:1.03–11.13; $P = 0.04$), older patients had a better OS (HR = 0.41; 95% CI:0.17–0.95; $P = 0.04$). After adjusting for age and disease stage, BRCA status was not associated with OS (HR = 0.51; 95% CI:0.23–1.17; $P = 0.11$) (Table 3).

Discussion

Our data indicate an overall 50% prevalence of deleterious BRCA1/2 mutations in a highly selected population of high-risk women with TNBC. To the best of our knowledge, this is the highest incidence of BRCA mutations reported up to date. We show that BRCA status does not adversely impact survival outcomes in patients with TNBC; in fact, BRCA carriers tend to have a decreased risk of breast cancer recurrence and death.

Clinically, the triple-negative or basal-like phenotype indicates the possible presence of a germline BRCA1 mutation. Few studies have assessed the mutation prevalence in women with TNBC who were selected for young age, FH or ethnic group, with reported rates of 24–29% [4, 15–17]. The BRCA1 mutation rate of 29% was among women with ER-negative, high-grade tumors who were diagnosed before the age of 35 [17]. Of note, only one of the BRCA1 carriers had a significant FH. Other observational studies have looked at the incidence of BRCA1/2 mutations in small selected cohorts of TNBC. Young et al. [18] examined 54 women with high-grade TNBC diagnosed at or before age 40 who had no significant FH; six (11%) of whom were found to carry BRCA mutations (five in BRCA1 and one in BRCA2). Similarly, in another study [19], the BRCA1 mutations were detected in 11.3% (20/177) of women with TNBC, and mutation prevalence was significantly higher than estimated by Myriad prevalence tables in the entire group. Furthermore, recent work from our institution showed a 19.5% BRCA mutation rate in an unselected patient cohort of TNBC, and almost half of the mutation carriers were not referred to genetic counseling or tested mostly due to having insufficient documented risks such as older age, lack of significant FH or insurance difficulties [20]. Kwon et al. [21] showed that interventions based on BRCA mutation testing results of women with TNBC who are younger than 50 years reduced subsequent breast and ovarian cancer risks by 23 and 41%, respectively. After these results, NCCN guidelines changed the criteria for further risk evaluation and now recommend referral for cancer genetic assessment in all individuals diagnosed with TNBC under the age of 60 [22].

Multiple studies have indicated that triple-negative and basal-like breast cancers, as a group, are associated with an adverse prognosis. During the first 5 years after diagnosis, there is a significantly increased risk for recurrence and death, but distant relapse after this time is much less common [23–26]. While most studies show a similar prognosis for women with hereditary breast cancers compared to age-matched women with sporadic breast cancers [10, 27–32], other studies have reported worse survival outcomes [33–37]. Notably, Cortesi et al. [38] reported a better prognosis in BRCA1 mutation carriers compared with BRCA mutation non-carriers and patients with sporadic breast cancer; OS estimates were 77% versus 77% versus 73%, respectively ($P < 0.001$). After adjustment for other patient characteristics, BRCA1 carriers had a significantly better OS (HR:0.29;95% CI:0.13–0.62, $P = 0.02$) compared with patients with sporadic breast cancer. More recently, consistent with our findings, Lee et al. [39] reported similar survival rates in BRCA1 mutation carriers with TN disease compared to non-carriers when treated with alkylating chemotherapy. These results suggest that deleterious BRCA1/2 mutations in TNBC do not carry an adverse prognostic significance.

Unlike HER2-positive breast cancer, currently there is no targeted biologic therapy available for TNBC, and endocrine therapy is not indicated. Thus, chemotherapy is currently the mainstay of systemic treatment. Although

Table 2 Univariate Cox proportional hazards model for recurrence-free survival and overall survival

	Recurrence-free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
BRCA status						
Positive vs. negative	0.70	0.40–1.23	0.22	0.52	0.23–1.19	0.12
Age						
>40 vs. ≤40	0.37	0.20–0.68	0.001	0.40	0.17–0.94	0.03
Premenopausal at diagnosis						
Yes vs. no	2.10	0.98–4.50	0.06	1.20	0.47–3.03	0.70
FH of BC						
Yes vs. no	0.73	0.39–1.35	0.31	0.62	0.27–1.45	0.27
Num rel with BC						
1 vs. 0	0.78	0.34–1.80	0.56	0.61	0.18–2.02	0.41
2 vs. 0	0.71	0.37–1.36	0.30	0.63	0.26–1.52	0.30
FH of OC						
Yes vs. no	1.01	0.54–1.88	0.97	1.64	0.73–3.66	0.23
Num rel with OC						
1 vs. 0	0.90	0.42–1.94	0.78	1.55	0.60–4.01	0.37
2 vs. 0	1.22	0.51–2.91	0.65	1.79	0.59–5.45	0.30
Nuclear grade						
3 vs. 1/2	1.13	0.34–3.68	0.83	0.57	0.17–1.96	0.38
Clinical stage						
II vs. I	1.69	0.73–3.92	0.22	1.44	0.46–4.47	0.53
III vs. I	4.35	1.81–10.43	0.001	3.78	1.16–12.3	0.03
Chemotherapy regimen						
A vs. AT	0.52	0.25–1.10	0.09	1.04	0.41–2.62	0.94
T vs. AT	1.58	0.38–6.53	0.53	1.89	0.25–14.6	0.54
Chemotherapy type						
Neoadjuvant vs. adjuvant	3.52	1.85–6.69	0.0001	4.47	1.75–11.4	0.002
Neither vs. adjuvant	0.37	0.05–2.71	0.33	0.70	0.09–5.12	0.70
Both vs. adjuvant	0.84	0.20–3.58	0.82	0.99	–	0.99
Surgery type						
BCS vs. mastectomy	0.89	0.51–1.58	0.59	1.12	0.51–2.45	0.79
Prophylactic mastectomy						
Yes vs. no	0.86	0.46–1.60	0.63	0.66	0.26–1.71	0.40
Prophylactic oophorectomy						
Yes vs. no	0.36	0.16–0.80	0.01	0.09	0.01–0.69	0.02

HR hazard ratio, *CI* confidence interval, *FH* family history, *BC* breast cancer, *OC* ovarian cancer, *Num rel with BC* number of relatives diagnosed with breast cancer, *Num rel with OC* number of relatives diagnosed with ovarian cancer, *AT* anthracycline–taxane-containing regimens, *A* anthracycline-based regimens without a taxane, *T* single-agent taxane, *BCS* breast conserving surgery

TNBC is biologically aggressive, chemotherapy improves the outcome to a greater extent when used in patients with TNBC than when used in patients with ER-positive subtypes [40]. Neoadjuvant studies have suggested that outcome is excellent in the minority of women with TNBC who achieve a complete pathological response (pCR); in contrast, the outcome for the majority who still have residual disease after treatment is relatively poor, reflecting the heterogeneity of triple-negative tumors [26]. Importantly, pCR rates in BRCA mutation-associated TNBC and non-BRCA mutation-associated TNBC were found to be similar [26, 41, 42], confirming molecular and pathological similarities between the triple-negative and BRCA mutant breast cancers. While studies reported superiority of anthracycline–taxane-containing regimens in TNBC [43, 44], there is no preferred standard form of chemotherapy for BRCA mutation-associated TNBC. Breast cancer cell lines with BRCA1/2 deficiency show profound hypersensitivity to apoptosis when treated with potent inhibitors of the enzyme poly (ADP-ribose) polymerase (PARP)

Table 3 Multivariate Cox proportional hazards model for recurrence-free survival and overall survival

	Recurrence-free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
BRCA status						
Positive vs. negative	0.67	0.38–1.19	0.17	0.51	0.23–1.17	0.11
Age						
>40 vs. ≤40	0.39	0.21–0.71	0.002	0.41	0.17–0.95	0.04
Clinical stage						
II vs. I	1.51	0.64–3.52	0.35	1.30	0.41–4.09	0.65
III vs. I	3.81	1.58–9.20	0.003	3.39	1.03–11.13	0.04

HR hazard ratio, *CI* confidence interval

[45–47], mitoxantrone, etoposide, cisplatin, and doxorubicin [48–51]. In our study, the fact that the outcomes were similar between BRCA carriers and non-carriers, most of whom received anthracycline–taxane-containing chemotherapy regimens, suggests that triple-negative BRCA mutant cancers are just as sensitive to conventional chemotherapy regimens as other high-grade TNBCs.

BPO is an effective means of reducing the risk of breast and ovarian cancer in carriers of both BRCA1 and BRCA2 mutations, especially if performed before age 40 [52–55]. Interestingly, the largest published cohort study showed that BPO was associated with a greater reduction in breast cancer risk for BRCA1 carriers (OR = 0.44; 95% CI:0.29–0.66; $P = 0.00006$) than for BRCA2 carriers (OR = 0.57; 95% CI:0.28–1.15; $P = 0.11$) [52]. A recent study provides evidence that BSO reduces not only cancer incidence but also all-cause mortality (HR = 0.38; 95% CI:0.24–0.62), breast cancer-specific mortality (HR = 0.38; 95% CI:0.20–0.72) and ovarian cancer-specific mortality (HR = 0.22;95% CI:0.06–0.83) [55]. The potentially larger risk reduction associated with BPO is of interest given the high proportion of ER-negative breast tumors in BRCA1 mutation carriers compared with BRCA2 mutation carriers. It is possible that estrogen deprivation after BPO confers a biologic effect as demonstrated by Zhang et al. [56] that estrogen signaling through the EGFR/Src/ERK pathway is involved in the development of ER-negative breast cancers. Larger data sets with longer follow-up are needed to define more precisely the reduction in mortality conferred by BPO.

Certain limitations of this study should be acknowledged. First, the relatively higher prevalence estimates in the current study can be explained by the highly select nature of our subject population, limiting generalizability of the findings to all patients. Second, examination of both BRCA1 and BRCA2 mutation groups together may have affected the survival outcomes as emerging data suggest that BRCA1 mutation carriers may experience differential benefits from interventions such as CPM or BPO compared with BRCA2 mutation carriers [55, 57, 58].

In conclusion, we found a high incidence of BRCA1/2 deleterious mutations among a highly selected population of high-risk women with TNBC, confirming that referral for BRCA genetic testing should be considered for women with TNBC. We also show that overall prognoses of patients with TNBC are similar between BRCA mutation carriers and non-carriers. Moreover, the present data support the common recommendation that women with TNBC and BRCA1/2 mutations should consider BPO once they have completed childbearing.

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Conflict of interest Authors have no financial interest to declare

References

1. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D (2000) Molecular portraits of human breast tumours. Nature 406:747–752
2. Rakha EA, Reis-Filho JS, Ellis IO (2008) Basal-like breast cancer: a critical review. J Clin Oncol 26:2568–2581
3. Bertucci F, Finetti P, Cervera N, Esterni B, Hermitte F, Viens P, Birnbaum D (2008) How basal are triple-negative breast cancers? Int J Cancer 123:236–240
4. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, Akslen LA (2003) Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 95:1482–1485
5. Lakhani SR, Reis-Filho JS, Fulford L, Penault-Llorca F, van der Vijver M, Parry S, Bishop T et al (2005) Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 11:5175–5180
6. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS et al (2003) Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 100:8418–8423
7. Reis-Filho JS, Tutt AN (2008) Triple negative tumours: a critical review. Histopathology 52:108–118

8. Nicoletto MO, Donach M, De Nicolo A, Artioli G, Banna G, Monfardini S (2001) BRCA-1 and BRCA-2 mutations as prognostic factors in clinical practice and genetic counselling. Cancer Treat Rev 27:295–304
9. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Begin LR, Offit K, Foulkes WD (2004) A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 6:R8–R17
10. Rennert G, Bisland-Naggan S, Barnett-Griness O, Bar-Joseph N, Zhang S, Rennert HS, Narod SA (2007) Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. N Engl J Med 357:115–123
11. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, Tung N, Olopade OI, Weber BL, McLennan J, Olivotto IA, Begin LR, Narod SA (2004) Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 10:2029–2034
12. Turner N, Tutt A, Ashworth A (2004) Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4:814–819
13. Singletary SE, Greene FL (2003) Revision of breast cancer staging: the 6th edition of the TNM Classification. Semin Surg Oncol 21:53–59
14. Black MM, Speer FD (1957) Nuclear structure in cancer tissues. Surg Gynecol Obstet 105:97–102
15. Chang J, Hilsenbeck SG, Sng JH, Wong J, Ragu GC (2001) Pathological features and BRCA1 mutation screening in premenopausal breast cancer patients. Clin Cancer Res 7:1739–1742
16. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, Harris L, Hait W, Toppmeyer D (2006) Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 24:5652–5657
17. Lidereau R, Eisinger F, Champeme MH, Nogues C, Bieche I, Birnbaum D, Pallud C, Jacquemier J, Sobol H (2000) Major improvement in the efficacy of BRCA1 mutation screening using morphoclinical features of breast cancer. Cancer Res 60:1206–1210
18. Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, Brooks KA, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, Narod SA (2009) The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 9:86
19. Kandel MJ, Stadler ZK, Masciari S et al (2006) Prevalence of BRCA1 mutations in triple negative breast cancer. Proc Am Soc Clin Oncol I 24:18S
20. Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, Potter J, Lanchbury JS, Stemke-Hale K, Hennessy BT, Arun BK, Hortobagyi GN, Do KA, Mills GB, Meric-Bernstam F (2011) Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17:1082–1089
21. Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, Arun B (2010) Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol 28:4214–4220
22. Oncology. (2011) NCCNNGi: genetic/familial high-risk assessment: breast and ovarian version 1
23. Tischkowitz M, Brunet JS, Begin LR, Huntsman DG, Cheang MC, Akslen LA, Nielsen TO, Foulkes WD (2007) Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 7:134
24. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, Nielsen TO (2008) Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 14:1368–1376
25. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13:4429–4434
26. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275–1281
27. Kennedy RDQJ, Johnston PH, Harkin DP (2002) BRCA1: mechanisms of inactivation and implications for management of patients. Lancet 360:1007–1014
28. Verhoog LC, Seynaeve C, Dahmen G, van Geel AN, Bartels CC et al (1999) Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 17:3396–3402
29. Brekelmans CT, Tilanus-Linthorst MM, Seynaeve C, vd Ouweland A, Menke-Pluymers MB, Bartels CC et al (2007) Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. B Eur J Cancer 43:867–876
30. Kriege M, Seynaeve C, Meijers-Heijboer H, Collee JM, Menke-Pluymers MB, Bartels CC et al (2008) Distant disease-free interval, site of first relapse and post-relapse survival in B. Breast Cancer Res Treat 111:303–311
31. Bonadona V, Dossart MS, Voirin N, Sinilnikova OM, Mignotte H, Mathevet P, Bremond A, Treilleux I, Martin A, Romestaing P et al (2007) Prognosis of early-onset breast cancer based on BRCA1/2 mutation status in a French population-based cohort and review. Breast Cancer Res Treat 101:233–245
32. Bordeleau L, Panchal S, Goodwin P (2010) Prognosis of BRCA-associated breast cancer: a summary of evidence. Breast Cancer Res Treat 119:13–24
33. Robson M, Lewin D, Federici M, Satagopan J, Bogolminy F, Heerdt A, Borgen P, McCormick B, Hudis C, Norton L, Boyd J, Offit K (1999) Breast conservation therapy for invasive breast cancer in Ashkenazi women with BRCA gene founder mutations. J Natl Cancer Inst 91:2112–2117
34. Chappuis PO, Kaputa L, Bégin LR, Wong N, Brunet JS, Narod SA, Slingerland J, Foulkes WD (2000) Germline BRCA1/2 mutations and p27 (Kip1) protein levels independently predict outcome after breast cancer. J Clin Oncol 18:4045–4052
35. Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, Gautier C, Gauthier-Villars M, Bourstyn E, Clough KB, Magdelenat H, Pouillart P, Vincent-Salomon A, Fourquet A, for the Institute Curie Breast Cancer Group, Asselian B (2000) Familial invasive breast cancer: worse outcome related to BRCA1 mutations. J Clin Oncol 18:4053–4059
36. Moller P, Evans DG, Reis MM, Gregory H, Anderson E, Maehle L, Lalloo F, Howell A, Apold J, Clark N, Lucassen A, Steel CM (2007) Surveillance for familial breast cancer: differences in outcome according to BRCA mutation status. Int J Cancer 121:1017–1020
37. Lee EH, Park SK, Park B, Kim SW, Lee MH, Ahn SH, Son BH, Yoo KY, Kang D (2010) Effect of BRCA1/2 mutation on short-term and long-term breast cancer survival: a systematic review and meta-analysis. Breast Cancer Res Treat 122:11–25
38. Cortesi L, Masini C, Cirilli C, Medici V, Marchi I, Cavazzini G, Pasini G, Turchetti D, Federico M (2010) Favourable ten-year overall survival in a Caucasian population with high probability of hereditary breast cancer. BMC Cancer 10:90
39. Lee LJ, Alexander B, Schnitt SJ, Comander A, Gallagher B, Garber JE, Tung N (2011) Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. Cancer 117:3093–3100

40. Colleoni M, Cole BF, Viale G, Regan MM, Price KN, Maiorano E, Mastropasqua MG, Crivellari D, Gelber RD, Goldhirsch A, Coates AS, Gusterson BA (2010) Classical cyclophosphamide, methotrexate, and fluorouracil chemotherapy is more effective in triple-negative, node-negative breast cancer: results from two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Clin Oncol 28:2966–2973
41. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, Perou CM (2007) The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329–2334
42. Arun B, Bayraktar S, Liu DD, Gutierrez-Barrera AM, Atchley D, Pusztai L, Litton J, Valero V, Meric-Bernstam F, Hortobagyi GN, Albarracin C (2011) Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and non-carriers: a single institution experience. J Clin Oncol (in press)
43. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, Broadwater G, Goldstein LJ, Martino S, Ingle JN, Henderson IC, Norton L, Winer EP, Hudis CA, Ellis MJ, Berry DA (2007) HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 357:1496–1506
44. Ellis P, Barrett-Lee P, Johnson L, Cameron D, Wardley A, O'Reilly S, Verrill M, Smith I, Yarnold J et al (2009) Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 373:1681–1692
45. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917–921
46. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, Helleday T (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. Nature 434:913–917
47. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, Giavara S, O'Connor MJ, Tutt AN, Zdzienicka MZ, Smith GC, Ashworth A (2006) Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 66:8109–8115
48. Abbott DW, Freeman ML, Holt JT (1998) Double-strand break repair deficiency and radiation sensitivity in BRCA2 mutant cancer cells. J Natl Cancer Inst 90:978–985
49. Husain A, He G, Venkatraman ES, Spriggs DR (1998) BRCA1 up-regulation is associated with repair-mediated resistance to cis-diamminedichloroplatinum (II). Cancer Res 58:1120–1123
50. Bhattacharyya A, Ear US, Koller BH, Weichselbaum RR, Bishop DK (2000) The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. J Biol Chem 275:23899–23903
51. Ren Q, Potoczek MB, Krajewski S, Krajewska M, Basu A, Haldar S, Reed JC, Turner BC (2001) Transcriptional regulation of the Bcl-2 gene by wild type BRCA1 is important in regulating response to DNA damage-induced apoptosis (abstract). Proc Am Assoc Cancer Res 42:2991
52. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, Weber B, Rebbeck T, Neuhausen SL, Ghadirian P, Foulkes WD, Gershoni-Baruch R, Friedman E, Rennert G, Wagner T, Isaacs C, Kim-Sing C, Ainsworth P, Sun P, Narod SA (2005) Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case–control study. J Clin Oncol 23:7491–7496
53. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL (2002) Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346:1616–1622
54. Struewing JP, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA (1995) Prophylactic oophorectomy in inherited breast/ovarian cancer families. J Natl Cancer Inst Monogr (17): 33–35
55. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R et al (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967–975
56. Zhang XT, Kang LG, Ding L, Vranic S, Gatalica Z, Wang ZY (2011) A positive feedback loop of ER-alpha36/EGFR promotes malignant growth of ER-negative breast cancer cells. Oncogene 30:770–780
57. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, Isaacs C, Evans DG, Lynch H, Eeles RA, Neuhausen SL, Daly MB, Matloff E, Blum JL, Sabbatini P, Barakat RR, Hudis C, Norton L, Offit K, Rebbeck TR (2008) Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 26:1331–1337
58. Rutter JL, Wacholder S, Chetrit A, Lubin F, Menczer J, Ebbers S, Tucker MA, Struewing JP, Hartge P (2003) Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. J Natl Cancer Inst 95:1072–1078