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HR-positive/HER2-negative breast cancer arising in patients with or without *BRCA2* mutation: different biological phenotype and similar prognosis

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Abstract

Background: *BRCA2* plays a key role in homologous recombination. However, information regarding its mutations in Chinese patients with breast cancer remains limited.

Objectives: This study aimed to assess the clinicopathological characteristics of *BRCA2* mutation breast cancer and explore the mutation's effect on hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer survival in China.

Design: This hospital-based cohort study prospectively included 629 women with breast cancer diagnosed from 2008 to 2023 at Zhejiang Cancer Hospital in China.

Methods: We compared the clinicopathological characteristics and metastatic patterns and analysed the invasive disease-free survival (iDFS), distant relapse-free survival (DRFS) and first-line progression-free survival (PFS1) of patients with HR-positive/HER2-negative breast cancer according to *BRCA2* mutations.

Results: Among the 629 patients, 78 had *BRCA2* mutations (12.4%) and 551 did not (87.6%). The mean age at diagnosis was lower in the *BRCA2* mutation breast cancer group than in the non-mutation breast cancer group (38.91 *versus* 41.94 years, $p = 0.016$). *BRCA2* mutation breast cancers were more likely to be lymph node-positive than non-mutation breast cancers (73.0% *versus* 56.6%, $p = 0.037$). The pathological grade was higher in 47.1% of *BRCA2* mutation breast cancers than in 29.6% of non-mutation breast cancers ($p = 0.014$). The proportions of patients with *BRCA2* mutations who developed contralateral breast cancer (19.2% *versus* 8.8%, $p = 0.004$), breast cancer in the family (53.8% *versus* 38.3%, $p = 0.009$) and ovarian cancer in the family (7.6% *versus* 2.4%, $p = 0.022$) were higher than those of patients without the mutation. The median follow-up time was 92.78 months. Multivariate analysis showed that *BRCA2* mutation was not associated with poorer iDFS [hazard ratio = 0.9, 95% confidence interval (CI) = 0.64–1.27, $p = 0.56$] and poorer distant relapse-free survival (DRFS) (hazard ratio = 1.09, 95% CI = 0.61–1.93, $p = 0.76$). There was no significant difference between the two groups with regard to metastatic patterns in the advanced disease setting. In the first-line metastatic breast cancer setting, PFS1 expression was broadly similar between the two groups irrespective of chemotherapy or endocrine therapy.

Conclusion: HR-positive/HER2-negative breast cancer with *BRCA2* mutations differs from those without mutations in clinical behaviour and reflects more aggressive tumour behaviour. Our results indicate that *BRCA2* mutations have no significant effect on the survival of Chinese women with HR-positive/HER2-negative breast cancer.

Keywords: *BRCA2*, breast cancer, HER2-negative, hormone receptor-positive, metastatic breast cancer, prognosis

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Introduction

Hereditary breast cancer accounts for approximately 5–10% of all breast cancer cases.[1] Breast cancer gene 1 (*BRCA1*) or breast cancer gene 2 (*BRCA2*) mutations are responsible for 50–60% of hereditary breast cancer cases.[2,3] In a large consecutive, unselected sample of 8627 Chinese patients with breast cancer, the *BRCA2* pathogenic germline mutation rate was 3.7%.[4]

BRCA2 mutation breast cancers are mainly hormone receptor (HR)-positive and human epidermal receptor 2 (HER2)-negative, and they are more likely to present as high histologic grade.[5,6] Generally, HR-positive breast cancers are characterized by a low pathological grade, late-onset and favourable prognosis.[7,8] However, several previous studies have found that patients with HR positivity with a *BRCA2* mutation have a higher rate of lymph node metastasis, an earlier age of onset and an adverse prognosis than do those without.[9–12] HR-positive breast cancers are currently treated with endocrine therapy combined with targeted therapies, including cyclin-dependent kinase 4 and 6 (CDK4/6), histone deacetylase and mammalian target of rapamycin (mTOR) inhibitors.[13,14] A recent study found that the loss of heterozygosity (LOH) of retinoblastoma 1 (*Rb1*) is frequent in breast cancers with a *BRCA2* germline mutation. LOH of *Rb1* correlates with resistance to CDK4/6 inhibitors.[15] Thus, the addition of CDK4/6 inhibitors to endocrine treatment may not be the optimal strategy for treating HR-positive and *BRCA2* mutation breast cancers.

Breast cancers exhibit specific patterns of recurrence and metastasis, which are mediated by factors such as molecular subtypes of cancers and host organ microenvironments.[16,17] The *BRCA2* mutation is related to central nervous system (CNS) metastasis and an increased risk of death.[18] In the pre-CDK4/6 inhibitors era, unless there was a visceral crisis, endocrine therapy was considered the preferred option for the first-line treatment of HR-positive/HER2-negative metastatic breast cancer (MBC).[19] *BRCA1/2* mutations are sensitive to cytotoxic chemotherapeutic agents.[20] Therefore, such agents should be considered for HR-positive/HER2-negative and *BRCA2* mutation breast cancers. However, data from metastatic settings are lacking.

Additionally, the oestrogen receptor (ER) signalling pathway is intrinsically linked to the BRCA2 protein. BRCA2 activates the ER signalling pathway, which conversely increases the expression of BRCA2.[21,22] Sustained DNA double-strand breaks are present in ER-positive breast cancer. Nevertheless, mutant BRCA2 proteins fail to repair broken double-stranded chains.[23] Therefore, breast cancers with *BRCA2* mutations may be more responsive to poly-ADP ribose polymerase (PARP) inhibitors, which inhibit DNA repair.

Consequently, HR-positive/HER2-negative and *BRCA2* mutation breast cancers may be specialized types that are distinct from sporadic HR-positive/HER2-negative breast cancers at the molecular level. However, studies on HR-positive/HER2-negative and *BRCA2* mutation breast cancers are lacking. The relationship between *BRCA2* mutation and predictive or prognostic value remains unclear. Whether the metastatic patterns of breast cancer are affected by the *BRCA2* mutation status is also uncertain. Therefore, we aimed to describe the clinicopathological features of HR-positive patients with and without a *BRCA2* mutation and investigate whether *BRCA2* mutation is an independent prognostic factor for HR-positive breast cancer in Chinese women.

Methods

Ethics statements

This study was approved by the Ethics Committee of the Zhejiang Cancer Hospital. All participants provided informed written consent.

Study design and patients

In this single-centre observational prospective study, we enrolled 1636 Chinese breast cancer patients at high genetic risk diagnosed at Zhejiang Cancer Hospital from February 2008 to June 2023. In total, 629 HR positive/HER2 negative were identified. The eligibility criteria were based on the National Comprehensive Cancer Network guidelines for genetic high-risk assessment of breast, ovarian and pancreatic cancers.[24] Patients were eligible for disease diagnosis at any time point. A flow chart of the study population is exhibited in Figure 1. The reporting of this study conforms to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Material 1).[25]

Data collection

Patients' information and tumour characteristics including age at first diagnosis, menopausal status

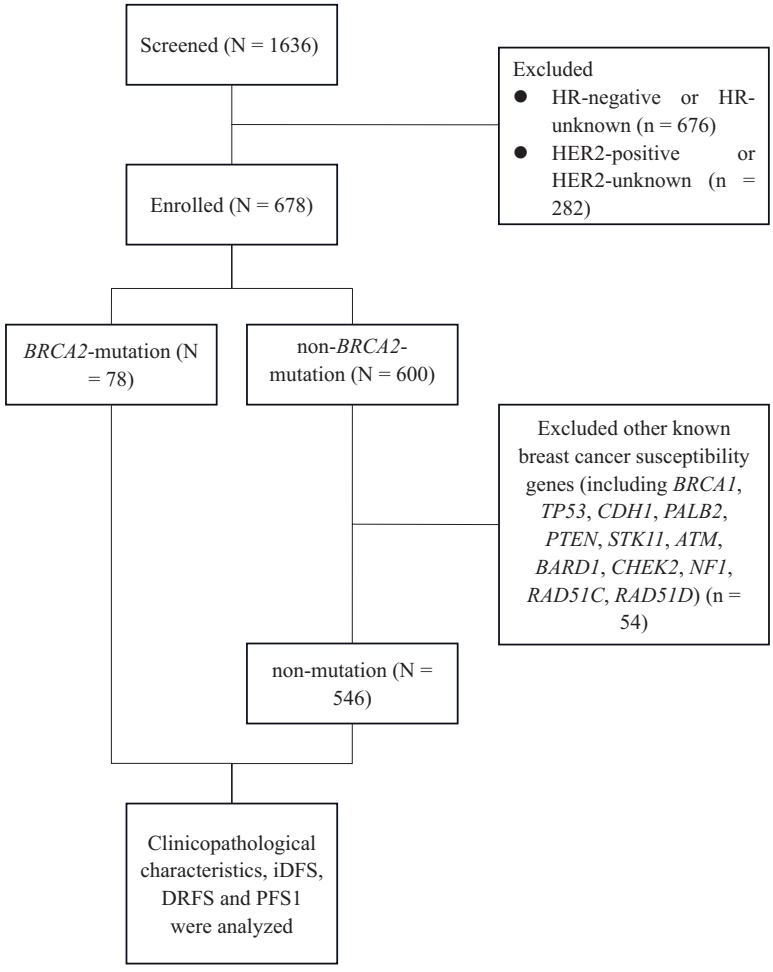

Figure 1. Flow chart of the study population.

at diagnosis, age of menopause, body mass index (BMI), T stage, lymph nodes status, pathological type, grade, vascular invasion, HER2 status, ER status, progesterone receptor (PR) status, surgical approach for primary tumours and lymph nodes, treatment with (neo)adjuvant chemotherapy and radiotherapy, endocrine therapy, first event in the advanced disease setting, visceral metastases, number of metastatic sites and first-line treatment were retrieved from the medical records and pathology reports of Zhejiang Cancer Hospital. Positive results for ER, PR and HER2 were defined as previously described.[26,27] Based on the prognostic impact of different pathological types,[28] we classified them as non-invasive carcinoma with good prognosis, invasive special carcinoma with good prognosis, invasive ductal carcinoma, invasive lobular carcinoma, other types with poor prognosis and others and unknown. *De novo* stage IV breast cancer was defined as metastasis diagnosed at the time of primary breast cancer diagnosis or within the adjuvant therapy period. The first events in the advanced disease setting were categorized as local, regional, brain, bone, liver and lung events. Local–regional recurrence was defined as the involvement of the ipsilateral breast, chest wall or lymph nodes.

Information on first-degree relatives and family history of tumours was obtained by interviewing the patients and asking them to report whether their family members, including parents, siblings and children, had ever been diagnosed with cancer and if so, to gain further information about which family member, what type of cancer and when the cancer was diagnosed.

Outcomes

The primary outcome was the comparison of invasive disease-free survival (iDFS) between

patients with *BRCA2* mutation breast cancer and those with non-mutation breast cancer. iDFS was defined as the time from diagnosis to the first occurrence of one of the following events: an ipsilateral invasive breast tumour, local invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer or death due to any cause. The secondary outcomes were distant relapse-free survival (DRFS) and first-line progression-free survival (PFS1) between the two groups of patients treated with first-line chemotherapy-based or only endocrine-based treatment. DRFS was calculated from the time of diagnosis to the first occurrence of distant recurrence or death due to any cause. PFS was measured from the time of starting first-line treatment to the first disease progression or death due to any cause.[29] Survival times were obtained from outpatient and telephone follow-ups.

BRCA2 *germline mutation screening*

Peripheral blood samples were obtained from the patients, and DNA samples were extracted using the QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany). We analysed the genetic variants in *BRCA2* using a 98-gene panel sequencing assay.[30] We focused on the overall exons and the 10-bp regions upstream and downstream of each exon in these genes. Based on ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), gnomAD (http://www.gnomad-sg.org/) and RefGene (https://annovar.openbioinformatics.org/en/latest/user-guide/download/) annotated by ANNOVA (24 October 2019, https://annovar.openbioinformatics.org/en/latest/), we classified all variants into different grades: pathogenic, likely pathogenic, variant of uncertain significance, likely benign and benign based on the American College of Medical Genetics guidelines. Pathogenic and likely pathogenic variants were classified as deleterious and analysed in this study.

Statistical analysis

The clinicopathological characteristics of patients were compared based on *BRCA2* germline mutation status using χ^2 tests or Fisher's exact test for categorical variables, and non-parametric Kruskal–Wallis' test for continuous variables. The Kaplan–Meier method was used for survival outcomes, and the log-rank test was used to evaluate differences. We calculated the median follow-up using the reverse Kaplan–Meier method. Hazard ratios and 95% confidence intervals (CIs) for univariate and multivariate analyses (for primary and secondary outcomes) were calculated using Cox proportional hazards models to identify independent factors influencing prognosis. The following prognostic variables were evaluated using univariate analyses for iDFS: *BRCA2* status (non-mutation/*BRCA2*), age at first diagnosis (continuous variables), T stage (Tis + T1/T2 + T3 + T4), lymph node status (N0; N1; N2 + N3), pathological type (non-invasive carcinoma with good prognosis + invasive special carcinoma with good prognosis/invasive ductal carcinoma + invasive lobular carcinoma + other types with poor prognosis), grade (I + II/III), vascular invasion (no/yes), HR status (ER+/PR+/ER+/PR− and ER−/PR+), surgical approach to primary tumours (breast-conserving surgery/mastectomy) and lymph nodes (sentinel node biopsy/axillary dissection), treatment with neoadjuvant (no/yes) and radiotherapy (no/yes) and endocrine therapy (no/yes). Variables yielding p values <0.05, determined by univariate analysis and *BRCA2* mutation status, were retained for multivariate analysis. The same assessment was performed for DRFS, with the exception that T stage was used with T1 as a reference and pathological type was used with invasive special carcinoma with good prognosis as a reference. Carcinoma *in situ* is not included in the DRFS analysis and is considered an early stage of breast cancer. In this stage, the cancer cells have not yet penetrated the basement membrane, and there is no lymphatic or vascular supply to the membrane, reducing the likelihood of distant metastasis. We performed a statistical assessment of the proportional hazard hypothesis. All analyses were two-tailed. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS software, version 25.0, or R software, version 3.3.1.

Results

Clinicopathological characteristics in BRCA2 *mutation breast cancer and non-mutation breast cancer*

Among the 629 patients with HR-positive/HER2-negative breast cancer, 78 had pathogenic germline *BRCA2* mutations and the remaining 551 did not have any mutations in other known breast cancer predisposition genes (including *BRCA1*, *TP53*, *ATM*, *RAD51C*, *RAD51D*, *PALB2*, *CHEK2*, *NF1*, *BARD1*, *PTEN*, *STK11*, *CDH1*).

Among *BRCA2* mutation carriers, one had an additional *CHEK2* mutation and five had other unidentified breast cancer susceptibility gene mutations.

A comparison of the clinicopathological characteristics between *BRCA2* mutation breast cancers and non-mutation breast cancers is shown in Table 1. The mean age of onset of patients with *BRCA2* mutation was lower than that of patients without the mutation (38.91 *versus* 41.94 years, $p = 0.016$). The proportion of patients with an initial diagnosis within 35 years of age was significantly higher in the *BRCA2* mutation group than in the non-mutation group (43.6% *versus* 28.6%, $p = 0.007$). Similarly, the mean age at menopause was lower in the *BRCA2* mutation group than in the non-mutation group (46.69 *versus* 50.48 years, $p = 0.006$). There was also no significant difference in BMI between the two groups. *BRCA2* mutation breast cancers were associated with a higher risk of developing contralateral breast cancer (19.2% *versus* 8.8%, $p = 0.004$), a higher family history of breast cancer (53.8% *versus* 38.3%, $p = 0.009$) and ovarian cancer (7.6% *versus* 2.4%, $p = 0.022$) compared with non-mutation breast cancers. There were no significant differences in personal history of ovarian cancer, personal history of ipsilateral breast cancer, personal/family history of gastrointestinal cancer and pancreatic cancer or family history of prostate cancer between the groups.

BRCA2 mutation breast cancers were more likely to be lymph node-positive than non-mutation breast cancers (73.0% *versus* 56.6%, $p = 0.037$). The percentage of breast cancers with a higher pathological grade was 47.1% among those with *BRCA2* mutations, compared to 29.6% among those without mutations ($p = 0.014$). The tumour size, pathological type and HR status were not significantly different between the two groups. Of the *BRCA2* mutation breast cancers, 41.3% were vascular invasion-positive, compared with 23.4% of non-mutation breast cancers ($p = 0.001$). Patients with *BRCA2* mutation were more often treated with mastectomies (88.4% *versus* 78.9%, $p = 0.003$) and axillary dissections than those without mutations (91.3% *versus* 68.9%, $p = 0.00$). Patients in the *BRCA2* mutation group were more likely to receive anthracycline combined with taxane chemotherapy regimens than single adjuvant chemotherapy. The percentage of patients receiving combination chemotherapy was lower in the non-mutation breast cancer group than in the *BRCA2* mutation breast cancer group (47.4% *versus* 62.1%, $p = 0.008$). There was no notable difference in the choice of radiotherapy or endocrine therapy between the two groups. The proportions of patients with *de novo* stage IV breast cancer were 11.5% among those with *BRCA2* mutation breast cancers and 7.3% among those with non-mutation breast cancers ($p = 0.196$).

Disease characteristics and treatments according to *BRCA2* mutation status in advanced disease settings are shown in Table 2. *BRCA2* mutation and non-mutation breast cancers most frequently had metastases to the bone (38.5% and 47.9%, respectively), followed by the lung (20.5% and 27.5%, respectively), liver (15.4% and 9.0%, respectively) and brain (2.6% and 2.8%, respectively). *BRCA2* mutation breast cancers showed a more evident trend towards metastasis than did non-mutation breast cancers (46.4% *versus* 41.7%, $p = 0.869$), although the p value was not significant. The number of metastatic sites at the initial diagnosis of MBC was not different between the two groups. Both groups mainly received chemotherapy or endocrine therapy alone as first-line treatment. Patients who received endocrine therapy after chemotherapy were included in the chemotherapy group. Only 9.5% of patients with non-mutation breast cancers received endocrine therapy with CDK4/6, mTOR or histone deacetylase inhibitors.

Prognosis and long-term survival

The median follow-up time was 92.78 months (range: 1–300 months). In all, 49 patients with an advanced initial diagnosis and 6 who were lost to follow-up were excluded from the analysis of iDFS. In total, 569 patients who were operable at the initial diagnosis had complete clinicopathological information for iDFS analysis, including 68 *BRCA2* mutation breast cancers and 501 non-mutation breast cancers. The median iDFS durations of *BRCA2* mutation breast cancer and non-mutation breast cancer were 91.21 and 87.71 months, respectively, and no significant difference was identified between the groups ($p = 0.56$) [Figure 2(a)]. HRs and 95% CIs were estimated after adjusting for tumour size, lymph nodes, grade, vascular invasion and *BRCA2* mutations. In multivariate analyses, no differences in iDFS were observed between the two groups, although there was a tendency for better iDFS in *BRCA2* mutation breast cancers than in

Table 1. Clinicopathological characteristics of HR-positive/HER2-negative breast cancer patients according to *BRCA2* mutation.

Characteristics	*BRCA2* mutation (*N* = 78)	Non-mutation (*N* = 546)	*p* Value
Age at diagnosis			
Mean (SD)	38.91 (8.82)	41.94 (10.55)	0.016
⩽35	34 (43.6%)	156 (28.6%)	0.007
>35	44 (56.4%)	390 (71.4%)	
⩽45	59 (75.6%)	378 (69.2%)	0.248
>45	19 (24.4%)	168 (30.8%)	
Menopausal status at diagnosis (excluded 10 males)			0.54
Pre	65 (83.3%)	431 (80.4%)	
Post	13 (16.7%)	105 (19.6%)	
Age of menopause (excluded 10 males)			0.006
Mean (SD)	46.69 (5.02)	50.48 (4.53)	
Oophorectomy/uterectomy/CIA	4	5	
Unknown	0	7	
Gender			0.622
Female	78 (100%)	536 (98.2%)	
Male	0	10 (1.8%)	
BMI			0.313
Mean (SD)	22.14 (3.31)	22.52 (2.88)	
Unknown	6	39	
Personal history of ovarian cancer (excluded 10 males)			0.559
Yes	1 (1.3%)	5 (0.9%)	
No	77 (98.7%)	531 (99.1%)	
Personal history of ipsilateral breast cancer			0.95
Yes	6 (7.7%)	52 (9.5%)	
No	72 (92.3%)	494 (90.5%)	
Personal history of contralateral breast cancer			0.004
Yes	15 (19.2%)	48 (8.8%)	
No	63 (80.8%)	498 (91.2%)	

(Continued)

Table 1. (Continued)

Characteristics	*BRCA2* mutation (*N* = 78)	Non-mutation (*N* = 546)	*p* Value
Personal history of gastric carcinoma			>0.999
Yes	0	1 (0.2%)	
No	78 (100%)	545 (99.8%)	
Family history of gastric carcinoma			0.425
Yes	6 (7.7%)	58 (10.6%)	
No	72 (92.3%)	488 (89.4%)	
Family history of breast cancer			0.009
Yes	42 (53.8%)	209 (38.3%)	
No	36 (46.2%)	337 (61.7%)	
Family history of ovarian cancer			0.022
Yes	6 (7.6%)	13 (2.4%)	
No	72 (92.4%)	533 (97.6%)	
Family history of pancreatic cancer			>0.999
Yes	1 (1.3%)	12 (2.2%)	
No	77 (98.7%)	534 (97.8%)	
Family history of prostate cancer			0.066
Yes	3 (3.8%)	5 (0.9%)	
No	75 (96.2%)	541 (99.1%)	
T stage			0.054
Tis	1 (1.5%)	20 (4.0%)	
T1	22 (33.8%)	249 (49.5%)	
T2	35 (53.8%)	200 (39.8%)	
T3	5 (7.7%)	19 (3.8%)	
T4	2 (3.1%)	15 (3.0%)	
Unknown	13	43	
Lymph nodes status			0.037
N0	20 (27.0%)	229 (43.4%)	
N1	26 (35.1%)	166 (31.4%)	
N2	14 (18.9%)	71 (13.4%)	
N3	14 (18.9%)	62 (11.7%)	
Unknown	4	18	

(Continued)

Table 1. (Continued)

Characteristics	*BRCA2* mutation (*N* = 78)	Non-mutation (*N* = 546)	*p* Value
Pathological type			0.635
Non-invasive carcinoma with a good prognosis	1 (1.3%)	20 (3.7%)	
Invasive special carcinoma with a good prognosis	4 (5.3%)	23 (4.2%)	
Invasive ductal carcinoma	63 (82.9%)	443 (81.6%)	
Invasive lobular carcinoma	5 (6.6%)	23 (4.2%)	
Other types with poor prognosis	3 (3.9%)	34 (6.3%)	
Other and unknown	2	3	
Grade			0.014
I	0	23 (6.1%)	
II	27 (52.9%)	243 (64.3%)	
III	24 (47.1%)	112 (29.6%)	
Unknown	27	168	
Vascular invasion			0
Yes	28 (43.1%)	111 (22.7%)	
No	37 (56.9%)	379 (77.3%)	
Unknown	13	56	
Hormone receptor status			0.325
ER+ and PR+	72 (92.3%)	470 (86.1%)	
ER+ and PR−	4 (5.1%)	58 (10.6%)	
ER− and PR+	2 (2.6%)	18 (3.3%)	
Surgery – primary tumour			0.003
Breast-conserving surgery	8 (11.6%)	141 (28.1%)	
Mastectomy	61 (88.4%)	361 (78.9%)	
None	0	0	
Unknown	0	4	
Surgery – lymphatic nodes			0
Sentinel node biopsy	6 (8.7%)	153 (30.5%)	
Axillary dissection	63 (91.3%)	346 (68.9%)	
None	0	3 (0.6%)	
Unknown	0	4	

(Continued)

Table 1. (Continued)

Characteristics	*BRCA2* mutation (*N* = 78)	Non-mutation (*N* = 546)	*p* Value
(Neo)Adjuvant chemotherapy			0.008
Anthracyclines	13 (19.7%)	112 (23.4%)	
Taxanes	5 (7.6%)	63 (13.2%)	
Anthracyclines + taxanes	41 (62.1%)	227 (47.4%)	
Other	4 (6.1%)	8 (1.7%)	
None	3 (4.5%)	69 (14.4%)	
Unknown	3	27	
Radiotherapy			0.407
Any	34 (63.0%)	270 (57.1%)	
None	30 (37.0%)	203 (42.9%)	
Unknown	5	33	
Adjuvant hormone therapy			0.898
TAM alone	30 (46.9%)	219 (46.6%)	
AI	29 (45.3%)	206 (43.8%)	
None	5 (7.8%)	45 (9.6%)	
Unknown	5	36	
De novo stage IV breast cancer			0.196
Yes	9 (11.5%)	40 (7.3%)	
No	69 (88.5%)	506 (92.7%)	

AI, aromatase inhibitors; CIA, chemotherapy-induced amenorrhea; TAM, tamoxifen.

non-mutation breast cancers (adjusted hazard ratio = 0.78, 95% CI = 0.46–1.32, $p = 0.37$) (Table 3).

In all, 21 patients with carcinoma *in situ* were excluded from the analysis of DRFS. In total, 548 patients with invasive breast cancer without metastasis had complete clinicopathological information for DRFS survival analysis (67 *BRCA2* mutation breast cancers and 481 mutation-free breast cancers). The median DRFS durations of *BRCA2* mutation breast cancers and non-mutation breast cancers were 139.31 and 109.79 months, respectively ($p = 0.19$) [Figure 2(b)]. In multivariate analyses (adjusted for tumour size, lymph nodes, grade, HR status, vascular invasion, the surgical approach for primary tumours, neoadjuvant chemotherapy and *BRCA2* mutation), *BRCA2* mutation breast cancers showed a similar DRFS compared to non-mutation breast cancers, although this did not reach statistical significance (hazard ratio = 1.09, 95% CI = 0.61–1.93, $p = 0.76$) (Table 4).

We further compared the differences in PFS1 between the two groups. When treated with chemotherapy as the first-line treatment, no apparent difference was detected between *BRCA2* mutation breast cancers and non-mutation breast cancers (median PFS1: 24.07 and 24.28 months, respectively). When treated with endocrine therapy for the first-line treatment, we also found a similar outcome between *BRCA2* mutation breast cancers and non-mutation breast cancers (median

Table 2. Patient and disease characteristics and treatment in the advanced disease setting according to *BRCA2* mutation.

Characteristics	*BRCA2* mutation (*N* = 28)	Non-mutation (*N* = 152)	*p* Value
First event			0.251
Local regional	9 (23.1%)	27 (12.8%)	
Brain	1 (2.6%)	6 (2.8%)	
Bone	15 (38.5%)	101 (47.9%)	
Liver	6 (15.4%)	19 (9.0%)	
Lung	8 (20.5%)	58 (27.5%)	
Visceral metastases			0.869
No	15 (53.6%)	84 (55.3%)	
Yes	13 (46.4%)	68 (41.7%)	
Number of metastatic sites			0.893
1	14 (50%)	81 (53.3%)	
2	6 (21.4%)	34 (22.4%)	
⩾3	8 (28.6%)	37 (24.3%)	
First-line treatment			0.204
Chemo/chemo sequenced by ET	14 (51.9%)	84 (57.5%)	
Chemo with immune	0	1 (0.7%)	
ET alone	13 (48.1%)	47 (32.2%)	
ET with CDK4/6 inhibitors/mTOR inhibitors/HDAC inhibitors	0	14 (9.6%)	
Unknown	1	6	

CDK, cyclin-dependent kinase; Chemo, chemotherapy; ET, endocrine therapy; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin.

PFS1: 15.51 and 16.96 months, respectively) (Figure 3).

Discussion

In this study, we investigated the differences in clinicopathological characteristics between patients with HR-positive/HER2-negative breast cancer with and without *BRCA2* mutation. Our study demonstrated that *BRCA2* mutation breast cancers had inferior clinicopathological characteristics compared to non-mutation breast cancers. We found that mutations in *BRCA2* were not associated with poorer iDFS and DRFS in the multivariate analysis. In the first-line MBC setting, PFS1 was broadly similar between the two groups irrespective of chemotherapy or endocrine therapy.

Our data showed that the mean age of *BRCA2* mutation breast cancer diagnosis was lower than that of non-mutation breast cancer and was consistent with the peculiarity of early onset in women with *BRCA2* mutation.[31,32] A review indicated that obesity is related to a higher risk of developing breast cancer and adverse breast cancer survival.[33] Our data showed no significant differences in the BMI between the two groups. Patients with *BRCA2* mutation breast cancer had a higher proportion of lymph node positivity,

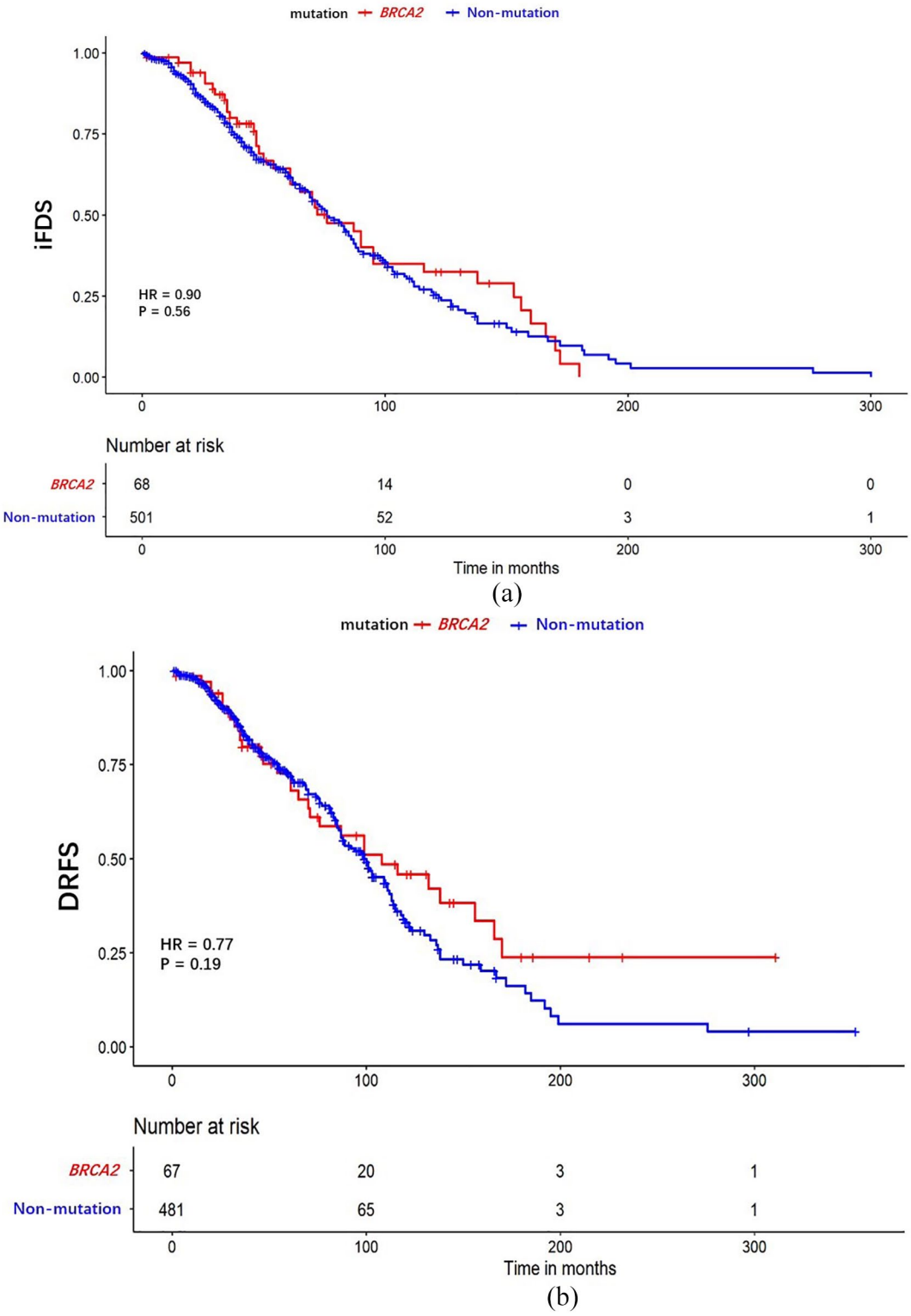

Figure 2. Comparison of iDFS (a) and DRFS (b) between *BRCA2* mutation breast cancer and non-mutation breast cancer.
DRFS, distant relapse-free survival; iDFS, invasive disease-free survival.

Table 3. Hazard ratios for iDFS from breast cancer for selected variables.

Variables	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age at diagnosis	0.99	0.98–1.01	0.75	NI		
BMI	1	0.96–1.04	0.91	NI		
T stage						
Tis + T1	1			1		
T2 + T3 + T4	1.87	1.40–2.5	0.00	1.95	1.29–2.94	0.001
Lymph nodes						
N0	1			1		
N1	1.31	0.95–1.82	0.09	1.27	0.79–2.05	0.31
N2 + N3	1.50	1.09–2.08	0.01	1.20	0.70–2.07	0.48
Pathological type						
Non-invasive carcinoma with good prognosis + invasive special carcinoma with good prognosis	1					
Invasive ductal carcinoma + invasive lobular carcinoma + other types with poor prognosis	0.83	0.48–1.44	0.52	NI		
Grade						
I + II	1			1		
III	1.72	1.21–2.45	0.002	1.61	1.07–2.41	0.01
Vascular invasion						
No	1					
Yes	1.47	1.07–2.01	0.01	1.13	0.73–1.75	0.57
Hormone receptor status						
ER+/PR+	1					
ER+/PR– and ER–/PR+	1.40	0.97–2.03	0.07	NI		
Surgery –primary tumour						
Breast-conserving surgery	1					
Mastectomy	1.17	0.82–1.68	0.37	NI		
Surgery – lymphatic nodes						
Sentinel node biopsy	1					
Axillary dissection	1.44	0.96–2.18	0.07	NI		
Adjuvant chemotherapy						
No	1					

(Continued)

Table 3. (Continued)

Variables	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Yes	0.97	0.63–1.49	0.89	NI		
Radiotherapy						
No	1					
Yes	0.94	0.72–1.22	0.64	NI		
Adjuvant hormone therapy						
No	1					
Yes	1.17	0.80–1.69	0.4	NI		
Mutation						
Non-mutation	1			1		
BRCA2	0.90	0.64–1.27	0.56	0.78	0.46–1.32	0.37

BMI, body mass index; *BRCA2*, breast cancer gene 2; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; iDFS, invasive disease-free survival; NI, not included; PR, progesterone receptor.

grade 3 tumours and vascular invasion than did patients with non-mutation breast cancer. These results are similar to those of several previous studies, indicating that *BRCA2* mutation breast cancers have more aggressive tumour features than non-mutation breast cancers do.[10,34] We observed that bilateral breast cancers were more frequent in patients with *BRCA2* mutation breast cancers than in those with non-mutation breast cancers. Similar findings were reported in a previous study.[35]

A recent study demonstrated that *BRCA2* pathogenic mutations are associated with an increased risk of seven cancers, including female breast, male breast, gastric, ovarian, pancreatic, prostate and oesophageal cancers.[36] We observed that patients with *BRCA2* mutation breast cancer were more likely to have a family history of breast or ovarian cancers. Unfortunately, our results did not demonstrate a relationship between *BRCA2* mutations and other cancer types. This may be attributed to the small number of patients with *BRCA2* mutation breast cancer, which lowered the statistical power.

In our cohort, patients with *BRCA2* mutation preferred mastectomy and axillary dissection to breast-conserving surgery and sentinel node biopsy. This may be because some patients and doctors were aware of their *BRCA2* mutation status before surgery. In germline *BRCA1/2* mutation breast cancers, breast-conserving surgery (BCT) is associated with a higher probability of local recurrence than mastectomy.[37] However, there is no difference in overall survival between BCT and mastectomy for germline *BRCA1/2* mutation breast cancers, and this therapy can improve the quality of life.[38]

Several studies have suggested that *BRCA2* mutations are associated with adverse prognostic significance in HR-positive breast cancers.[11,39–42] Moreover, the prognosis varies between races, and there is still a lack of large-sample research in China. Remarkably, our results suggest that *BRCA2* mutations have no significant effect on the survival of Chinese women with HR-positive/HER2-negative breast cancer. After adjusting for several main prognostic factors, a tendency towards prolonged iDFS was observed, although the difference was not statistically significant. Most patients in our study population received anthracycline-based adjuvant chemotherapy. Adjuvant chemotherapy may improve patients' outcomes. These results imply that *BRCA2*-deficient tumours are more sensitive to chemotherapy regimens, causing DNA breaks due to homologous recombination defects.[43,44]

Table 4. Hazard ratios for DRFS from breast cancer for selected variables.

Variables	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age at diagnosis	0.98	0.97–1.00	0.11	NI		
BMI	0.99	0.95–1.04	0.92	NI		
T stage						
T1	1			1		
T2 + T3 + T4	2.08	1.48–2.92	0.00	2.10	1.23–3.58	0.006
Lymph nodes						
N0	1			1		
N1	1.14	0.77–1.70	0.49	1.18	0.63–2.23	0.58
N2 + N3	1.94	1.34–2.81	0.00	1.13	0.58–2.21	0.70
Pathological type						
Invasive special carcinoma with a good prognosis	1					
Invasive ductal carcinoma + invasive lobular carcinoma + other types with poor prognosis	1.68	0.68–4.10	0.25	NI		
Grade						
I + II	1			1		
III	1.79	1.21–2.66	0.003	1.65	1.03–2.64	0.03
Vascular invasion						
No	1			1		
Yes	1.53	1.07–2.18	0.017	1.51	0.90–2.52	0.11
HR status						
ER+ and PR+	1			1		
ER+ or PR+	1.54	1.02–2.31	0.036	1.32	0.68–2.58	0.40
Surgery – primary tumour						
Breast-conserving surgery	1			1		
Mastectomy	1.69	1.05–2.74	0.03	1.52	0.75–3.09	0.23
Surgery – lymphatic nodes						
Sentinel node biopsy	1					
Axillary dissection	1.38	0.82–2.29	0.216	NI		
Adjuvant chemotherapy						
No	1			1		
Yes	2.21	1.08–4.51	0.029	2.34	0.71–7.71	0.16

(Continued)

Table 4. (Continued)

Variables	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Radiotherapy						
No	1					
Yes	1.15	0.85–1.55	0.35	NI		
Adjuvant hormone therapy						
No	1					
Yes	0.81	0.54–1.23	0.336	NI		
Mutation						
Non-carriers	1			1		
BRCA2	0.77	0.52–1.14	0.194	1.09	0.61–1.93	0.76

BMI, body mass index; CI, confidence interval; DRFS, distant relapse-free survival; ER, oestrogen receptor; HR, hazard ratio; NI, not included; PR, progesterone receptor.

DNA damage drugs such as PARP inhibitors, alkylating agents, topoisomerase II inhibitors and platinum are promising strategies for treating HR-positive/HER2-negative and *BRCA2* mutation breast cancer, as they have shown high efficacy in *BRCA2* mutation breast cancer, whether alone or in combination with other drugs.[20,45,46] A retrospective study indicated that HR-positive and germline *BRCA1/2* mutation breast cancers had Oncotype DX recurrence risk scores approximately three times higher than those of non-mutation breast cancers.[47] Therefore, these drugs should be included among the choices for adjuvant treatment. The OlympiA study demonstrated that 1 year of adjuvant intensive therapy with the PARP inhibitor olaparib significantly improved the 3-year iDFS in patients with mutations in the *BRCA1* or *BRCA2* genes.[48] In HR-positive/HER2-negative breast cancer patients, the 3-year iDFS rates were 83.5% and 77.2% in the olaparib and placebo groups, respectively. Based on the results of this trial, the 2021 American Society of Clinical Oncology guideline updated the recommendation that suggested providing 1 year of adjuvant olaparib to patients with early-stage HER2-negative and *BRCA* mutation breast cancer who had finished chemotherapy and local therapy.[49] Because of the poor response to CDK4/6i,[50,51] PARP inhibitors could be the preferred first-line treatment choice in patients with HR-positive/HER2-negative MBC carrying a *BRCA2* mutation, which is an explorable issue that deserves more clinical trials to address. Furthermore, experiments have confirmed that *BRCA2*-deficient breast cancer cells respond more strongly to immune checkpoint inhibitors (ICIs).[52] Denkert *et al.*[53] demonstrated that pathological complete response rates increased as tumour-infiltrating lymphocytes increased in luminal-HER2-negative breast cancer, indicating the potential effectiveness of immunotherapy. PARP inhibitors combined with ICIs have also demonstrated favourable performance in the management of HR-positive and *BRCA2* mutation breast cancers.[54] Furthermore, well-designed studies are warranted to validate these findings.

Several studies have shown that HR-positive breast cancers are more prone to bone metastasis, which was also reflected in our study population.[55,56] Song *et al.*[18] demonstrated that *BRCA2* mutation breast cancers have a higher frequency of CNS metastasis than non-mutation breast cancers do, which was not reflected in our results. The study by Frenel *et al.*[57] demonstrated that HR-positive/HER2-negative and *BRCA2* mutation breast cancers exhibit lower tumour sensitivity to first-line endocrine therapy than non-mutation breast cancers do, but not to first-line chemotherapy. We sought to validate this in our data; however, our results showed no difference in PFS1 between the two groups when receiving first-line endocrine therapy. The discrepancies in results could have been caused by several reasons. First, the enrolled population in the study by Frenel *et al.* included both *BRCA1* and *BRCA2* mutation breast cancer.

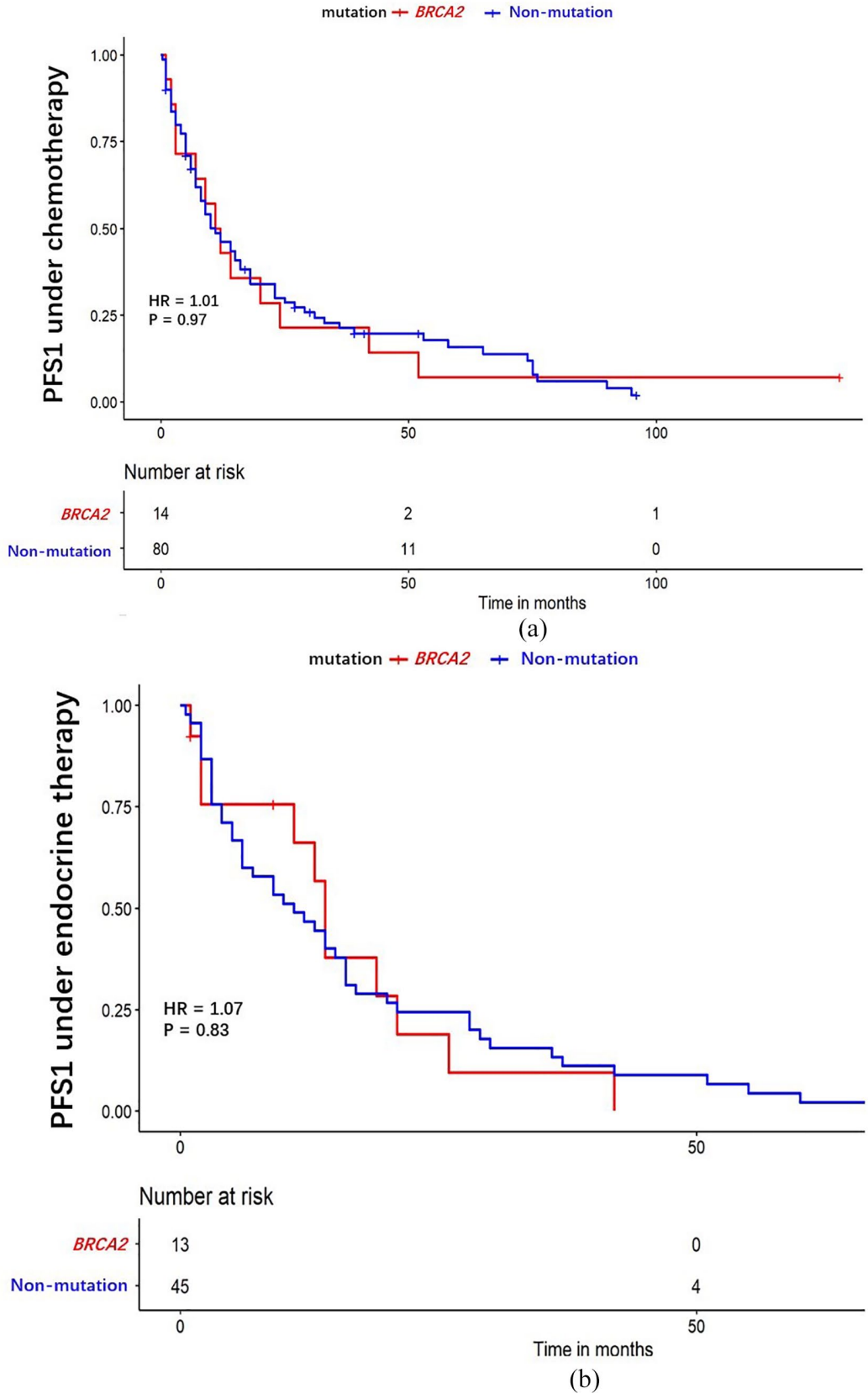

Figure 3. PFS1 for patients receiving first-line chemotherapy (a) or endocrine therapy (b) according to *BRCA2* mutation.
BRCA2, breast cancer gene 2; PFS1, first-line progression-free survival.

Our study population consisted solely of breast cancer patients with *BRCA2* mutation. Because *BRCA1* or *BRCA2* mutation may differentially affect breast cancer sensitivity to endocrine therapy,[51] it is possible that combining these two groups obscured the distinction. Second, our study was limited by the small number of *BRCA2* mutation breast cancers for PFS1 analysis, which may have influenced the results and reduced statistical power. Finally, the number of visceral metastases at first-line treatment was higher in the *BRCA1/2* mutation group than in the non-mutation group (67.6% *versus* 56.7%, $p=0.0003$) in the study by Frenel *et al.*, which may have led to a worse PFS1 than that in the non-mutation group; conversely, there was no difference in the number of visceral metastases between the two groups in our study (46.4% *versus* 41.7%, $p=0.869$). Whether *BRCA2* mutation reduces sensitivity to endocrine therapy remains unclear.

Our study has several advantages. A multitude of previous studies of Chinese women were limited by their small sample sizes. Our sample size was large, and the follow-up time was long. Moreover, we detected all the coding regions and exon–intron boundaries of the genes and had adequate details on the family history of cancer and clinicopathological characteristics. The limitations of this study include an insufficient number of patients with *BRCA2* mutation breast cancer. Another significant limitation of the study is that it was conducted at a single centre, which may have led to selection bias. Most of the patients were from Zhejiang Province, China, and breast cancer may show variation in different geographic populations. Future studies involving larger sample sizes and multi-centre collaborations will yield more comprehensive results. Moreover, we did not obtain the complete overall survival data.

In summary, *BRCA2* mutation breast cancers differ from non-mutation breast cancers in terms of their clinical behaviour. Our study may have implications for the genetic counselling and administration of *BRCA2* mutation breast cancers. Our evidence does not support a clear effect of *BRCA2* status on survival in HR-positive/HER2-negative breast cancers. Nevertheless, routine *BRCA2* gene testing is necessary for patients with breast cancer due to the availability of chemotherapeutic and targeted agents resulting in DNA breaks that are therapeutically effective. All conclusions drawn from this study need to be treated with caution and confirmed in a larger population. Given the strides in gene sequencing and personalized medicine, an increasing number of breast cancer patients with a *BRCA2* mutation have been identified. In this era of personalized medicine, individuals with HR-positive/HER2-negative breast cancer and a *BRCA2* mutation should receive more tailored and precise treatment.

Conclusion

In conclusion, breast cancer patients with a *BRCA2* mutation exhibited distinct clinical characteristics compared to those without mutations in our cohort. They showed more aggressive tumour behaviour, including earlier onset, higher lymph node involvement, higher pathological grade and an elevated risk of contralateral breast cancer, familial breast cancer and familial ovarian cancer. The *BRCA2* germline mutations do not significantly impact the prognosis of HR-positive/HER2-negative early breast cancer patients or the effectiveness of first-line treatment for MBC. This study offers a justification for the clinical management of *BRCA2* mutation breast cancer, and the findings should be validated in a larger sample.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Zhejiang Cancer Hospital (protocol code IRB-2017–1999, 7 December 2017). All participants provided informed written consent.

Consent for publication

Not applicable.

Author contributions

Pu-Chun Li: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Yi-Fan Zhu: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Jia-Ni Pan: Data curation; Investigation; Methodology.

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Xiao-Wen Ding: Funding acquisition; Investigation; Resources.

Lin-Feng Zheng: Conceptualization; Methodology; Supervision; Writing – review & editing.

Wen-Ming Cao: Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material
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References

1. Castéra L, Krieger S, Rousselin A, *et al.* Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet* 2014; 22: 1305–1313.
2. Stratton MR and Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet* 2008; 40: 17–22.
3. Antoniou AC and Easton DF. Models of genetic susceptibility to breast cancer. *Oncogene* 2006; 25: 5898–5905.
4. Zang F, Ding X, Chen J, *et al.* Prevalence of BRCA1 and BRCA2 pathogenic variants in 8627 unselected patients with breast cancer: stratification of age at diagnosis, family history and molecular subtype. *Breast Cancer Res Treat* 2022; 195: 431–439.
5. Mavaddat N, Barrowdale D, Andrulis IL, *et al.* Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012; 21: 134–147.
6. Spurdle AB, Couch FJ, Parsons MT, *et al.* Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. *Breast Cancer Res* 2014; 16: 3419.
7. Grann VR, Troxel AB, Zojwalla NJ, *et al.* Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. *Cancer* 2005; 103: 2241–2251.
8. Yoon KH, Park Y, Kang E, *et al.* Effect of estrogen receptor expression level and hormonal therapy on prognosis of early breast cancer. *Cancer Res Treat* 2022; 54: 1081–1090.
9. Tryggvadottir L, Olafsdottir EJ, Olafsdottir GH, *et al.* Tumour diploidy and survival in breast cancer patients with BRCA2 mutations. *Breast Cancer Res Treat* 2013; 140: 375–384.
10. Jonasson JG, Stefansson OA, Johannsson OT, *et al.* Oestrogen receptor status, treatment and breast cancer prognosis in Icelandic BRCA2 mutation carriers. *Br J Cancer* 2016; 115: 776–783.
11. Vocka M, Zimovjanova M, Bielcikova Z, *et al.* Estrogen receptor status oppositely modifies breast cancer prognosis in BRCA1/BRCA2 mutation carriers *versus* non-carriers. *Cancers (Basel)* 2019; 11: 738.
12. Evans DG, Phillips KA, Milne RL, *et al.* Survival from breast cancer in women with a BRCA2 mutation by treatment [published correction appears in *Br J Cancer* 2023; 128: 703]. *Br J Cancer* 2021; 124: 1524–1532.

13. Sledge GW Jr, Toi M, Neven P, *et al*. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol* 2020; 6: 116–124.

14. Yamamoto-Ibusuki M, Arnedos M and André F. Targeted therapies for ER+/HER2− metastatic breast cancer. *BMC Med* 2015; 13: 137.

15. Safonov A, Bandlamudi C, de Lara PT, *et al*. Comprehensive genomic profiling of patients with breast cancer identifies germline-somatic interactions mediating therapy resistance [abstract]. In: *Proceedings of the 2021 San Antonio Breast Cancer Symposium, San Antonio, TX, 7–10 December 2021*. Philadelphia, PA: AACR, America.

16. Kennecke H, Yerushalmi R, Woods R, *et al*. Metastatic behavior of breast cancer subtypes. *J Clin Oncol* 2010; 28: 3271–3277.

17. Chen W, Hoffmann AD, Liu H, *et al*. Organotropism: new insights into molecular mechanisms of breast cancer metastasis. *NPJ Precis Oncol* 2018; 2: 4.

18. Song Y, Barry WT, Seah DS, *et al*. Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers. *Cancer* 2020; 126: 271–280.

19. Cardoso F, Paluch-Shimon S, Senkus E, *et al*. 5th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC5). *Ann Oncol* 2020; 31: 1623–1649.

20. Mylavarapu S, Das A and Roy M. Role of BRCA mutations in the modulation of response to platinum therapy. *Front Oncol* 2018; 8: 16.

21. Jin W, Chen Y, Di GH, *et al*. Estrogen receptor (ER) beta or p53 attenuates ERalpha-mediated transcriptional activation on the BRCA2 promoter. *J Biol Chem* 2008; 283: 29671–29680.

22. Suba Z. DNA stabilization by the upregulation of estrogen signaling in BRCA gene mutation carriers. *Drug Des Devel Ther* 2015; 9: 2663–2675.

23. Williamson LM and Lees-Miller SP. Estrogen receptor α-mediated transcription induces cell cycle-dependent DNA double-strand breaks. *Carcinogenesis* 2011; 32: 279–285.

24. Daly MB, Pal T, Berry MP, *et al*. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021. *JNCCN J Natl Compr Cancer Netw* 2021; 19: 77–102.

25. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.

26. Allison KH, Hammond MEH, Dowsett M, *et al*. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol* 2020; 38: 1346–1366.

27. Yao L, Liu Y, Li Z, *et al*. HER2 and response to anthracycline-based neoadjuvant chemotherapy in breast cancer. *Ann Oncol* 2011; 22: 1326–1331.

28. Chinese Anti-Cancer Association Breast Cancer Professional Committee. Chinese anti-cancer association breast cancer diagnosis and treatment guidelines and standards. *Chin J Cancer* 2021; 31: 954–1040.

29. Gourgou-Bourgade S, Cameron D, Poortmans P, *et al*. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) [published correction appears in *Ann Oncol* 2015; 26: 2505–2506]. *Ann Oncol* 2015; 26: 873–879.

30. Zhu L, Pan JN, Qian Z, *et al*. High chromosome instability identified by low-pass whole-genome sequencing assay is associated with TP53 copy loss and worse prognosis in BRCA1 germline mutation breast cancer. *Breast Cancer* 2022; 29: 103–113.

31. Engel C and Fischer C. Breast cancer risks and risk prediction models. *Breast Care (Basel)* 2015; 10: 7–12.

32. Kim J and Oktay K. Baseline E(2) levels are higher in BRCA2 mutation carriers: A potential target for prevention? *Cancer Causes Control* 2013; 24: 421–426.

33. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, *et al*. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. *CA Cancer J Clin* 2017; 67: 378–397.

34. Olafsdottir EJ, Borg A, Jensen MB, *et al*. Breast cancer survival in Nordic BRCA2 mutation carriers – unconventional association with oestrogen receptor status. *Br J Cancer* 2020; 123: 1608–1615.

35. Kuchenbaecker KB, Hopper JL, Barnes DR, *et al*. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317: 2402–2416.

36. Momozawa Y, Sasai R, Usui Y, *et al*. Expansion of cancer risk profile for BRCA1 and BRCA2 pathogenic variants. *JAMA Oncol* 2022; 8: 871–878.

37. Davey MG, Davey CM, Ryan ÉJ, *et al.* Combined breast conservation therapy *versus* mastectomy for BRCA mutation carriers – a systematic review and meta-analysis. *Breast* 2021; 56: 26–34.

38. Wan Q, Su L, Ouyang T, *et al.* Comparison of survival after breast-conserving therapy vs mastectomy among patients with or without the BRCA1/2 variant in a large series of unselected Chinese patients with breast cancer. *JAMA Netw Open* 2021; 4: e216259.

39. Schmidt MK, van den Broek AJ, Tollenaar RA, *et al.* Breast cancer survival of BRCA1/BRCA2 mutation carriers in a hospital-based cohort of young women. *J Natl Cancer Inst* 2017; 109: 1–10.

40. Metcalfe K, Lynch HT, Foulkes WD, *et al.* Oestrogen receptor status and survival in women with BRCA2-associated breast cancer. *Br J Cancer* 2019; 120: 398–403.

41. Lambertini M, Ceppi M, Hamy AS, *et al.* Clinical behavior and outcomes of breast cancer in young women with germline BRCA pathogenic variants. *NPJ Breast Cancer* 2021; 7: 16.

42. Goodwin PJ, Phillips KA, West DW, *et al.* Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an international prospective breast cancer family registry population-based cohort study. *J Clin Oncol* 2012; 30: 19–26.

43. Deans AJ and West SC. DNA interstrand crosslink repair and cancer. *Nat Rev Cancer* 2011; 11: 467–480.

44. Tung N, Arun B, Hacker MR, *et al.* TBCRC 031: randomized phase II study of neoadjuvant cisplatin *versus* doxorubicin-cyclophosphamide in germline BRCA carriers with HER2-negative breast cancer (the INFORM trial). *J Clin Oncol* 2020; 38: 1539–1548.

45. Lee KH, Sohn J, Goodwin A, *et al.* Talazoparib *versus* chemotherapy in patients with HER2-negative advanced breast cancer and a germline BRCA1/2 mutation enrolled in Asian countries: exploratory subgroup analysis of the phase III EMBRACA trial. *Cancer Res Treat* 2021; 53: 1084–1095.

46. Ayoub JP, Wildiers H, Friedlander M, *et al.* Safety and efficacy of veliparib plus carboplatin/paclitaxel in patients with HER2-negative metastatic or locally advanced breast cancer: subgroup analyses by germline BRCA1/2 mutations and hormone receptor status from the phase-3 BROCADE3 trial. *Ther Adv Med Oncol* 2021; 13: 17588359211059601.

47. Halpern N, Sonnenblick A, Uziely B, *et al.* Oncotype Dx recurrence score among BRCA1/2 germline mutation carriers with hormone receptors positive breast cancer. *Int J Cancer* 2017; 140: 2145–2149.

48. Tutt ANJ, Garber JE, Kaufman B, *et al.* Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med* 2021; 384: 2394–2405.

49. Tung NM, Zakalik D and Somerfield MR; Hereditary Breast Cancer Guideline Expert Panel. Adjuvant PARP inhibitors in patients with high-risk early-stage HER2-negative breast cancer and germline BRCA mutations: ASCO Hereditary Breast Cancer Guideline rapid recommendation update. *J Clin Oncol* 2021; 39: 2959–2961.

50. Collins JM, Nordstrom BL, McLaurin KK, *et al.* A real-world evidence study of CDK4/6 inhibitor treatment patterns and outcomes in metastatic breast cancer by germline BRCA mutation status. *Oncol Ther* 2021; 9: 575–589.

51. Zattarin E, Taglialatela I, Lobefaro R, *et al.* Breast cancers arising in subjects with germline BRCA1 or BRCA2 mutations: different biological and clinical entities with potentially diverse therapeutic opportunities. *Crit Rev Oncol Hematol* 2023; 190: 104109.

52. Samstein RM, Krishna C, Ma X, *et al.* Mutations in BRCA1 and BRCA2 differentially affect the tumor microenvironment and response to checkpoint blockade immunotherapy. *Nat Cancer* 2021; 1: 1188–1203.

53. Denkert C, von Minckwitz G, Darb-Esfahani S, *et al.* Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol* 2018; 19: 40–50.

54. Domchek SM, Postel-Vinay S, Im SA, *et al.* Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. *Lancet Oncol* 2020; 21: 1155–1164.

55. Lin NU, Claus E, Sohl J, *et al.* Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer* 2008; 113: 2638–2645.

56. Wang R, Zhu Y, Liu X, *et al.* The clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer* 2019; 19: 1091.

57. Frenel JS, Lusque A, Delaloge S, *et al.* Efficacy of front-line treatment for hormone receptor-positive HER2-negative metastatic breast cancer with germline BRCA1/2 mutation. *Br J Cancer* 2023; 128: 2072–2080.