Changing Patterns in Clinicopathological Characteristics of Breast Cancer and Prevalence of *BRCA1* Mutations: Analysis in a Rural Area of Southern China

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Purpose: Although the burden of breast cancer remains especially high in rural China, data on the clinicopathological characteristics and prevalence of the breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations in patients with breast cancer remain limited. We investigated the clinicopathological characteristics, changing patterns, and prevalence of *BRCA1/2* mutations in patients with breast cancer.

Patients and Methods: The clinicopathological characteristics of 3712 women with pathologically confirmed primary breast cancer treated at Meizhou People's Hospital between January 2005 and December 2018 were evaluated. The prevalence of *BRCA1/2* mutations in 340 patients with breast cancer diagnosed between January 2017 and September 2018 was also evaluated.

Results: The median age at diagnosis was 49±10.5 (range, 20–94) years. Positivity for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was observed in 59.0%, 52.5%, and 24.9% of patients, respectively. Time trend analysis revealed that an increasing trend was observed for age at diagnosis ($p = 0.001$), proportion of patients without a reproductive history ($p < 0.001$), postmenopausal patients ($p = 0.001$), invasive pathological cancer type ($p = 0.008$), ER-positive rate ($p < 0.001$), PR-positive rate ($p = 0.008$), and HER2-positive rate ($p < 0.001$). Compared with patients without *BRCA1/2* mutations, those with *BRCA1/2* mutations were more likely to have a family history of breast or ovarian cancer ($p < 0.001$) and have triple-negative breast cancer (TNBC) ($p < 0.001$). Family history of breast or ovarian cancer (odds ratio [OR], 103.58; 95% confidence interval [CI], 20.58–521.45; $p < 0.001$) and TNBC subtype (OR, 5.97; 95% CI, 1.16–30.90; $p = 0.033$) were independent predictors for *BRCA1/2* mutation.

Conclusion: The clinicopathological characteristics of patients with breast cancer in this rural area have changed during the past decade. *BRCA1/2* testing should be performed in patients with breast cancer with a family history of breast or ovarian cancer and TNBC.

Keywords: *BRCA1/2* mutation, breast neoplasm, molecular subtype, stage

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Introduction

Breast cancer is the most common malignancy among women in urban areas of China and second most common malignancy among women in rural areas. In recent years, the incidence of breast cancer has increased in China, and the extent of the increase is greater in the countryside.^{1,2} The disparities of clinical outcomes, such as presentation, treatment

strategies, and survival, between patients with breast cancer in the city and countryside have long been reported.^{3–9} Due to the socioeconomic disparities, patients with breast cancer in rural areas face more difficulties with access to a high level of cancer care and preventive services.^{3,6} They are more likely to present with a later disease stage, lower reconstruction rates, and lower overall survival rates than their urban counterparts.^{7–9} As a developing country, the population living in the countryside makes up more than one-third of the Chinese population. The disparities in China may be even more extreme.

Breast cancer is a heterogeneous disease. Each subtype has a distinct molecular mechanism, presents with unique clinical presentation and prognosis, and responds differently to treatments. Understanding the diversity of gene expression can better predict survival and the treatment efficacy in patients with breast cancer.¹⁰ Breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations are closely related to the occurrence and development of breast cancer and can also predict the treatment effect of platinum-based chemotherapy and poly-adenosine diphosphate-ribose polymerase inhibitors (PARPis).^{11–13} Patients with breast cancer with *BRCA1/2* mutations display distinctive clinical features: a family history of breast or ovarian cancer, younger age at diagnosis, or triple-negative cancer subtype.¹⁴ Most large-scale studies on the clinicopathological characteristics of *BRCA*-associated breast cancer have been on Western patients, while studies on Asian populations have been small and sporadic.

Limited data are available regarding the clinicopathological characteristics of and prevalence of *BRCA1/2* mutations in patients with breast cancer in rural China. Therefore, this study aimed to investigate the clinicopathological characteristics of, changing patterns in, and prevalence of *BRCA1/2* mutations in patients with breast cancer admitted to Meizhou People's Hospital, which is located in the mountainous region of eastern Guangdong Province, southern China. The results are expected to provide a reference for the prevention and control of breast cancer.

Materials and Methods

Data Sources

Patient cohorts in this study are presented in Figure 1. Female patients were included if they were newly diagnosed with primary breast cancer at Meizhou People's Hospital, Meizhou, China, between January 1, 2005 and December 31, 2018. Patients with unknown stage, occult

breast cancer, or primary history of other cancer were excluded. Clinicopathological data, including age at diagnosis; menopausal status; reproductive history; stage; pathological type; estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses; and treatment strategies, were collected from patients' medical records. Finally, 3712 patients with breast cancer were included. We had not assessed *BRCA1/2* mutations until 2017. Due to the high costs of the next-generation sequencing test, not all patients could be tested. Only 340 patients had the test performed between 2017 and 2018.

Molecular Subtypes and Tumor Staging

The ER, PR, and HER2 statuses were assessed by board-certified pathologists in the Department of Pathology at Meizhou People's Hospital based on immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) findings. ER and PR positivity were defined as $\geq 1\%$ positive tumor cells with nuclear staining. ER and PR negativity was defined as $<1\%$ positive tumor cells with nuclear staining. Hormone receptor (HR) positivity was defined as either ER or PR positivity, and HR negativity was defined as both ER and PR negativity. HER2 positivity was defined as an IHC staining score of 3+ or gene amplification detected using FISH. HER2 negativity was defined as an IHC staining score of 0/1+ or a negative FISH result. HER2 IHC (2+) without FISH was categorized as "unknown". Patients with breast cancer were classified as HR-positive (HR+)/HER2-negative (HER2–), HR+/HER2-positive (HER2+), HR-negative (HR–)/HER2– (triple-negative breast cancer [TNBC]), HR–/HER2+, or "unknown" according to HR and HER2 expression. Staging was categorized based on the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging system during diagnosis.¹⁵

BRCA1/2 Mutation Testing

Next-generation sequencing was used to test the peripheral blood samples of 340 patients with breast cancer for *BRCA1/2* mutations between January 2017 and September 2018. Two milliliters of peripheral blood samples were collected from each participant. Genomic DNA was extracted from leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's instructions. The quality of the DNA was quantified using NanodropTM 2000 spectrophotometer (ThermoFisher Scientific, Waltham, MA), and good quality DNA samples were stored at -80°C until

Figure 1 Patient cohort selection in this study.

analyzed. A DNA library was constructed using the IonPlus Fragment Library Kit (Life Technologies, Carlsbad, CA), and semiconductor sequencing was performed using an Ion Proton instrument (Life Technologies). High-throughput sequencing and bioinformatics analysis were used to detect the presence of *BRCA1* and *BRCA2* gene mutations in subjects. In this study, pathogenic mutation, likely pathogenic mutation, mutation with uncertain significance, and benign mutation were named according to the Human Genome Variation Society guidelines using the following reference sequences: *BRCA1* (LRG_292t1, NM_007294.3) and *BRCA2* (LRG_293t1, NM_000059.3). Deleterious *BRCA1/2* mutations were considered pathogenic and likely pathogenic mutations.

Statistical Analyses

A descriptive analysis of clinicopathological data of 3712 female patients with breast cancer was performed. The

frequency of each characteristic was calculated for all patients, including those with missing data. Patients were divided into five groups according to their year of diagnosis as follows: 2005–2009, 2010–2012, 2013–2014, 2015–2016, and 2017–2018. Changes in patterns of characteristics between these five periods were analyzed. The time trend of age at diagnosis was evaluated using a one-way analysis of variance. The time trend of other clinicopathological characteristics was analyzed using a linear-by-linear association test. The difference in categorical variables between the *BRCA1/2* mutation-positive and -negative groups were compared using chi-squared tests or Fisher's exact test. Age at diagnosis was compared using a one-way analysis of variance. AJCC stage distribution was compared using the Mann–Whitney *U*-test. Binary logistic regression was performed to evaluate the relationship between the *BRCA1/2* mutation and

clinicopathological characteristics. A p -value < 0.05 was considered statistically significant. However, a p -value threshold of ≤ 0.2 was used in the univariate analysis for inclusion of *BRCA 1/2* mutation risk factors in the multivariate analysis. Statistical analyses were performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA).

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences. Before *BRCA* mutation testing, written informed consent was obtained from all participants.

Results

Changing Patterns in Clinicopathological Characteristics

The clinicopathological characteristics of the 3712 patients with breast cancer included in this study are summarized in Table 1. The mean age at diagnosis was 49.9 ± 10.5 (range, 20–94) years. Patients without a reproductive history accounted for 1.1%. The proportion of women who were postmenopausal was 39.5%. The most common pathological type was invasive ductal carcinoma (91.8%), followed by invasive lobular carcinoma (2.1%), mucinous carcinoma (1.6%), ductal carcinoma in situ (DCIS)/lobular carcinoma in situ (LCIS) (1.5%), medullary carcinoma (0.8%), and “others” (2.3%). The most common TNM stage was stage II (48.6%), followed by stage III (27.6%), stage I (17.1%), stage IV (5.2%), and stage 0 (DCIS/LCIS, 1.5%). The proportions of ER+ and PR+ patients were 59.0% and 52.5%, respectively. In total, 923 (24.9%) patients were HER2+. HR+/HER2– breast cancer was the most common molecular subtype (44.1%), followed by HR–/HER2– (15.5%), HR–/HER2+ (13.4%), and HR+/HER2+ (11.5%).

Table 1 also summarizes the time trend of breast cancer during 2005–2018. An increasing trend was observed in age at diagnosis ($p = 0.001$), proportion of patients with no reproductive history ($p < 0.001$), postmenopausal patients ($p = 0.001$), invasive pathological type ($p = 0.008$), ER-positive rate ($p < 0.001$), PR-positive rate ($p = 0.008$), and HER2-positive rate ($p < 0.001$). However, the proportion of AJCC stage ($p = 0.878$) and molecular subtype ($p = 0.707$) did not reach statistical significance ($p > 0.05$). The trends for T stage, N stage, and treatment strategies

were also analyzed (Supplementary Table S1). An increasing trend was observed in the proportion of T1 stage cancer, breast-conserving surgery, sentinel lymph node biopsy, neoadjuvant therapy, trastuzumab treatment, adjuvant radiotherapy, and endocrine therapy. The proportion of N stage and chemotherapy did not reach statistical significance ($p > 0.05$).

Prevalence of *BRCA1/2* Mutations

Three hundred forty patients with breast cancer were tested for *BRCA1/2* mutations. Deleterious *BRCA1/2* mutations were found in 3.8% (13/340) of patients. Five patients (5/340, 1.5%) had *BRCA1* mutations, and eight (8/340, 2.4%) had *BRCA2* mutations. Among those 13 patients, 10 had pathogenic mutations and three had likely pathogenic mutations. Among the 13 *BRCA1/2* mutations, the most prevalent mutation type was a frameshift mutation (6/13, 46.2%), followed by nonsense mutation (4/13, 30.8%), missense mutation (2/13, 15.4%), and intron mutation (1/13, 7.7%).

Compared with patients without *BRCA1/2* mutation, patients with *BRCA1/2* mutation were more likely to have a family history of breast or ovarian cancer ($p < 0.001$) and more likely to have TNBC ($p < 0.001$) (Table 2). According to the univariate logistic regression analysis, family history ($p < 0.001$) and TNBC ($p = 0.013$) were significantly related to *BRCA1/2* mutation (Table 3). These factors and HER2 status ($p = 0.082$) were included in the multivariate logistic regression analysis (Table 3). The results showed that family history of breast cancer or ovarian cancer (odds ratio [OR], 103.58; 95% confidence interval [CI], 20.58–521.45; $p < 0.001$) and TNBC subtype (OR, 5.97; 95% CI, 1.16–30.90; $p = 0.033$) were independent predictors for *BRCA1/2* mutation (Table 3).

Discussion

In this study, we found that the clinicopathological characteristics of patients with breast cancer in our area had significantly changed during the past decades. The age at diagnosis had increased, and more patients with postmenopausal status were diagnosed. The positive rates of ER, PR, and HER2 had also increased. However, the distribution of TNM stage had not changed, and the proportion of invasive carcinoma was still very high. The deleterious *BRCA1/2* mutation rate was 3.8% in our study. A family history of breast or ovarian cancer and TNBC subtype were independently associated with *BRCA1/2* mutation in patients with breast cancer.

Table I Characteristics of Female Patients with Breast Cancer and Changes in Trends Between 2005 and 2018

	Year										p-value	Total (n=3712)	
	2005–2009 (n=716)		2010–2012 (n=706)		2013–2014 (n=721)		2015–2016 (n=768)		2017–2018 (n=801)				
Age at diagnosis, years	48.3±10.9		49.8±11.0		50.3±11.3		50.3±10.9		50.4±10.5		0.001 ^a	49.9±10.5	
Reproductive history, n (%)											<0.001 ^b		
No	1	(0.1)	5	(0.7)	10	(1.4)	9	(1.2)	16	(2.0)		41	(1.1)
Yes	715	(99.9)	701	(99.3)	711	(98.6)	759	(98.8)	785	(98.0)	3671	(98.9)	
Menopausal status, n (%)											0.001 ^b		
Premenopausal	475	(66.3)	424	(60.1)	433	(60.1)	452	(58.9)	461	(57.6)		2245	(60.5)
Postmenopausal	241	(33.7)	282	(39.9)	288	(39.9)	316	(41.1)	340	(42.4)	1467	(39.5)	
Pathological type, n (%)											0.008 ^b		
Invasive ductal carcinoma	644	(89.9)	641	(90.8)	672	(93.2)	701	(91.3)	748	(93.4)		3406	(91.8)
Invasive lobular carcinoma	20	(2.8)	9	(1.3)	12	(1.7)	21	(2.7)	16	(2.0)	78	(2.1)	
Invasive carcinoma, other type	37	(5.2)	44	(6.2)	26	(3.6)	34	(4.4)	30	(3.7)	170	(4.6)	
DCIS/LCIS	15	(2.1)	12	(1.7)	11	(1.5)	12	(1.6)	7	(0.9)	57	(1.5)	
AJCC stage, n (%)											0.878 ^b		
0	15	(2.1)	12	(1.7)	11	(1.5)	11	(1.4)	7	(0.9)		56	(1.5)
I	70	(9.8)	111	(15.7)	139	(19.3)	147	(19.2)	171	(21.4)	638	(17.2)	
II	399	(55.7)	365	(51.7)	337	(46.7)	335	(43.6)	368	(45.9)	1804	(48.6)	
III	210	(29.3)	201	(28.5)	203	(28.2)	223	(29.0)	185	(23.1)	1022	(27.5)	
IV	22	(3.1)	17	(2.4)	31	(4.3)	52	(6.8)	70	(8.7)	192	(5.2)	
ER status, n (%)											<0.001 ^b		
Negative	300	(41.9)	277	(39.2)	257	(35.6)	214	(27.9)	260	(32.5)		1308	(35.2)
Positive	331	(46.2)	395	(56.0)	439	(60.9)	514	(66.9)	511	(63.8)	2190	(59.0)	
Unknown ^c	85	(11.9)	34	(4.8)	25	(3.5)	40	(5.2)	30	(3.7)	214	(5.8)	
PR status, n (%)											0.008 ^b		
Negative	286	(39.9)	322	(45.6)	294	(40.8)	288	(37.5)	360	(44.9)		1550	(41.7)
Positive	345	(48.2)	350	(49.6)	402	(55.7)	440	(57.3)	411	(51.3)	1948	(52.5)	
Unknown ^c	85	(11.9)	34	(4.8)	25	(3.5)	40	(5.2)	30	(3.8)	214	(5.8)	
HER2 status, n (%)											<0.001 ^b		
Negative	382	(53.4)	469	(66.4)	418	(58.0)	480	(62.5)	464	(57.9)		2213	(59.6)
Positive	132	(18.4)	124	(17.6)	185	(25.6)	211	(27.5)	271	(33.8)	923	(24.9)	
Unknown ^c	202	(28.2)	113	(16.0)	118	(16.4)	77	(10.0)	66	(8.3)	576	(15.5)	
Molecular subtype, n (%)											0.707 ^b		
HR+/HER2–	261	(36.5)	325	(46.0)	308	(42.7)	385	(50.1)	357	(44.6)		1636	(44.1)
HR+/HER2+	63	(8.8)	46	(6.5)	83	(11.5)	107	(13.9)	127	(15.8)	426	(11.5)	
HR–/HER2–	121	(16.9)	144	(20.4)	110	(15.3)	95	(12.4)	107	(13.4)	577	(15.5)	
HR–/HER2+	69	(9.6)	78	(11.1)	102	(14.1)	104	(13.6)	144	(18.0)	497	(13.4)	
Unknown ^c	202	(28.2)	113	(16.0)	118	(16.4)	77	(10.0)	66	(8.2)	576	(15.5)	

Notes: ^aOne-way analysis of variance. ^bLinear-by-linear association. ^cThese cases were not included in the analysis.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor; AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

The number of patients with breast cancer admitted to our hospital has continually increased in recent years. Studies^{16–19} have shown that many factors can increase the risk of breast cancer, and more Chinese women are at risk in both rural and urban areas.^{20,21} In this study, the

mean age at diagnosis was 49.9±10.5 years, with premenopausal women accounting for 60.5% of the cases. However, we found that age at diagnosis and the proportion of postmenopausal patients had increased over time, in agreement with results of previous studies.^{1,22} Invasive

Table 2 Difference in Characteristics Between Patients with Breast Cancer with BRCA1/2 Mutation and without BRCA1/2 Mutation

	BRCA1/2 M (-)		BRCA1/2 M (+)		p-value
Age, years (median, interquartile range)	48.3±9.3		43.2±7.5		0.053 ^a
Family history of breast or ovarian cancer					<0.001 ^b
No	322	(98.5%)	6	(46.2%)	
Yes	5	(1.5%)	7	(53.8%)	
ER status					0.589 ^c
Negative	114	(34.9%)	6	(46.2%)	
Positive	213	(65.1%)	7	(53.8%)	
PR					0.633 ^c
Negative	154	(47.1%)	7	(53.8%)	
Positive	173	(52.9%)	6	(46.2%)	
HER2 status					0.062 ^c
Negative	192	(58.7%)	11	(84.6%)	
Positive	135	(41.3%)	2	(15.4%)	
Molecular subtypes					0.075 ^c
HR+/HER2-	151	(46.2%)	6	(46.2%)	
HR+/HER2+	66	(20.2%)	1	(7.7%)	
HR-/HER2-	41	(12.5%)	5	(38.5%)	
HR-/HER2+	69	(21.1%)	1	(7.7%)	
TNBC					0.023 ^c
No	286	(87.5%)	8	(61.5%)	
Yes	41	(12.5%)	5	(38.5%)	
AJCC stage					0.841 ^d
I	53	(16.2%)	1	(7.7%)	
II	150	(45.9%)	8	(61.5%)	
III	99	(30.3%)	4	(30.8%)	
IV	25	(7.6%)	0	(0.0%)	

Notes: ^aOne-way analysis of variance, ^bFisher's exact test, ^cchi-square test, ^dMann-Whitney U-test.

Abbreviations: BRCA, breast cancer susceptibility gene; M, mutation; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor; TNBC, triple-negative breast cancer; AJCC, American Joint Committee on Cancer.

ductal carcinoma was the most prevalent pathological subtype in this region. Patients who were diagnosed with DCIS/LCIS accounted for <2.0% of the cases. These findings were in agreement with those of another study²³ of patients with breast cancer in the neighboring Chaoshan area. However, compared with breast cancer cases in Japan, South Korea, and the urban areas of China, there were more cases of invasive breast cancer and fewer cases of DCIS/LCIS in this region.^{22,24,25} Furthermore, a greater proportion of patients in this study presented with more advanced breast cancer (stages III and IV, 32.9%), and N0 tumors only accounted for 47.1% of the cases. The prevalence of nodal involvement has remained high in recent years. Although there was a steady increase in the

proportion of patients presenting with stage I breast cancer, the proportion of patients presenting with stage III disease remained high, and there was an increase in the proportion of patients presenting with stage IV disease. Moreover, the proportion of patients with carcinoma in situ in this region has not increased in the last 14 years. The women in this rural area do not have access to regular breast cancer screening and have substandard awareness of breast cancer prevention, which may contribute to a more invasive pathological type and advanced presentation.

The ER+ rate (59.0%) was lower in patients with breast cancer in this study than in those from urban areas of China, South Korea, Japan, and the USA.^{4,14,16,17} This

Table 3 Multivariate Logistic Regression Analysis of Possible Factors Independently Predicting *BRCA1/2* Mutation

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, years			0.264	/	/	/
<50	Ref.	Ref.		/	/	/
≥50	0.51	0.15–1.67		/	/	/
Family history of breast or ovarian cancer			<0.001			<0.001
No	Ref.	Ref.		Ref.	Ref.	
Yes	75.13	18.47–305.69		103.58	20.58–521.45	
T stage			0.944	/	/	/
T1+T2	Ref.	Ref.		/	/	/
T3+T4	1.06	0.23–4.92		/	/	/
LNM			0.978	/	/	/
Negative	Ref.	Ref.		/	/	/
Positive	1.02	0.33–3.17		/	/	/
ER status			0.407	/	/	/
Negative	Ref.	Ref.		/	/	/
Positive	0.62	0.21–1.90		/	/	/
PR status			0.633	/	/	/
Negative	Ref.	Ref.		/	/	/
Positive	0.76	0.25–2.32		/	/	/
HER2 status			0.082			0.432
Negative	Ref.	Ref.		Ref.	Ref.	
Positive	0.26	0.06–1.19		0.47	0.07–3.10	
TNBC			0.013			0.033
No	Ref.	Ref.		Ref.	Ref.	
Yes	4.36	1.36–13.97		5.97	1.16–30.90	

Abbreviations: BRCA, breast cancer susceptibility gene; OR, odds ratio; CI, confidence interval; LNM, lymph node metastasis; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor; TNBC, triple-negative breast cancer.

may be related to the greater proportion of premenopausal patients with breast cancer in our study. However, the proportion of patients with ER+ breast cancer in this region has increased in recent years, which is similar to the trend observed in previous studies.^{4,22,25} Although the exact cause is unclear, studies^{17,26} suggest that the trend may be related to increased levels of obesity and lower fertility rates. In our study, we found a trend of a decrease in the fertility rate. Meanwhile, a recent study²⁷ also found that there was a steady increase in the mean body mass index and obesity prevalence of women in rural areas in China during 2004–2018. These findings may in some way contribute to the increase in ER-positive rates. We should pay more attention to these risk factors in future studies. The HER2+ rate in this study was 24.9%, which is

consistent with that of previous reports in China and other Asian countries^{22,24,25} but is higher than that reported by studies conducted in the USA.⁴ These differences in the receptor expression of breast cancer across countries may be attributed to variations in the prevalence of risk factors²⁶ and genetic predisposition.²⁸ In addition, they may be attributed to selection bias because of the study design.

Individuals who harbor germline *BRCA1/2* mutations have a predisposition to breast cancer. In this study, the deleterious *BRCA1/2* mutation rate was 3.8%. The most prevalent type of the *BRCA1/2* mutation in our study was a frameshift mutation, followed by a nonsense mutation, missense mutation, and intron mutation, in line with findings of a previous study on a Chinese population.²⁹

A family history of breast or ovarian cancer and the TNBC subtype were independent predictors for *BRCA1/2* mutations. These results are also consistent with those reported in previous studies.^{11,30,31} However, the large CIs that are present in our study may be related to the limited sample size. Future studies with a larger sample size are needed to better illustrate the predictive value of these risk factors. *BRCA1/2* mutations can also predict the treatment effect of platinum-based chemotherapy¹² and PARPis, such as olaparib,¹³ in the treatment of metastatic breast cancer. A recent study³² showed that patients with high-risk early breast cancer and *BRCA1/2* mutations could also benefit from 1 year of olaparib treatment after completion of standard adjuvant therapy. However, *BRCA1/2* mutation may not be the only indicator of efficacy in olaparib treatment. Studies have shown that homologous recombination deficiency, high tumor-infiltrating lymphocyte counts, or high programmed death-ligand 1 expression are related to olaparib response in addition to *BRCA1/2* mutation.^{33,34} These findings are important for managing TNBC, a heterogeneous subtype with an unfavorable prognosis and no effective treatment. More relevant studies are needed to better identify candidates for PARPis treatment among patients with TNBC.

The single-center retrospective design of our study may have introduced several biases and limitations. First, the number of patients with breast cancer in this area may have been underestimated because patients who had been hospitalized in other hospitals of the region were not included. Second, critical data were missing in the records of patients diagnosed before 2010, such as data on HR and HER2 status. Finally, in the absence of regular follow-ups, survival data and treatment outcomes of these patients could not be presented.

Conclusion

This study showed that the clinicopathological characteristics of patients with breast cancer in this rural area have changed. However, a large number of patients still have locally advanced or metastatic disease and invasive pathology. Family history of breast cancer or ovarian cancer and TNBC subtype were independent predictors for *BRCA1/2* mutation. Strategies should be adopted to help people adhere to a healthy lifestyle and to increase public awareness regarding the importance of early breast cancer detection. *BRCA1/2* testing should be performed for patients with breast cancer with a family history of breast cancer or ovarian cancer or who have TNBC.

Abbreviations

BRCA1/2, Breast cancer susceptibility gene 1/2; CI, Confidence interval; DCIS, ductal carcinoma in situ; ER, Estrogen receptor; FISH, Fluorescence in situ hybridization; HR, Hormone receptor; LCIS, Lobular carcinoma in situ; OR, Odds ratio; PR, Progesterone receptor; TNBC, Triple-negative breast cancer.

Data Sharing Statement

The datasets used and/or analyzed in the current study will be available from the corresponding author upon reasonable request immediately after article publication and for a period of 5 years.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences (Ethical approval number: 2016-A-29). Before *BRCA1/2* mutation testing, written informed consent was obtained from all the patients.

Consent for Publication

The author confirms that its publication has been approved by all co-authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; drafted or wrote or substantially revised or critically reviewed the article; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agreed to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors report no conflicts of interest in this work.

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