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Clinicopathologic Factors Related to the Histological Tumor Grade of Breast Cancer in Western China: An Epidemiological Multicenter Study of 8619 Female Patients

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Abstract

BACKGROUND AND PURPOSE: Breast cancer is now recognized as a clinically heterogeneous disease with a wide spectrum of epidemiological and clinicopathologic features. We aimed to evaluate whether epidemiological and clinicopathologic features are associated with the histological tumor grade of breast carcinomas in Western China. *METHODS:* We retrospectively collected data from the Western China Clinical Cooperation Group and assessed associations between clinicopathologic factors and histological tumor grade in 8619 female breast cancer patients. Patients were divided into two groups: Group I (tumor grade I/II) and Group II (tumor grade III). Univariable analysis and multivariable logistic regression models were used to analyze the relationships between clinicopathologic factors and tumor grade. *RESULTS:* Patients presenting with positive axillary lymph nodes, large tumor size (>2 cm), lymphovascular invasion, hormone receptor negativity, human epidermal growth factor receptor 2 (HER-2) positivity, and triple negativity tended to have an increased risk of a high tumor grade. However, the number of pregnancies or births was inversely correlated with the risk of a high tumor grade. In addition, patients presenting with grade III tumors were more likely to receive aggressive treatment, such as adjuvant chemotherapy, anti–HER-2 therapy, and level III axillary lymph node dissection. *CONCLUSIONS:* Our results suggested that several clinicopathologic factors were associated with high tumor grade of breast cancer patients in Western China.

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Introduction

Breast cancer is the most common type of cancer among females worldwide, comprising almost 25% of all cancer cases among females [1]. Breast cancer is also the second leading cause of cancer-related mortality in women worldwide [1,2]. In recent years, many risk factors for breast cancer have been explored extensively among females in developed countries [3,4]. However, little is known about the risk factors that affect the biological behavior of breast cancer among females in Western China. Due to the less developed social and economic background in Western China, limited information is available regarding the epidemiology, diagnosis, and treatment of breast cancer in this region. Thus, there is an urgent need for epidemiological and clinical studies that identify risk factors associated with the biological characteristics of breast carcinomas in Western China.

Western China refers to the western part of China, which includes 12 provinces. It accounts for 71% of the land area and 29% of the population of China. This region used to be described as "barren, remote and poor." Compared with people living in Eastern China, people living in Western China might have different lifestyles, such as eating habits and health awareness. Our previous study showed that there were significant differences in the clinicopathologic features, risk factors, and treatment modes between younger and older female breast cancer patients in Western China [5]. Therefore, it is reasonable to assume that breast cancer patients with different histological tumor grades might have specific epidemiological and clinicopathologic characteristics.

Histological tumor grade is widely recognized as a marker for aggressive biological behavior of breast cancer carcinomas [6]. Moreover, it is generally acknowledged that a higher tumor grade is directly related to poorer prognosis of breast cancer patients [7]. Previous studies have shown that pathologic factors, such as human epidermal growth factor receptor 2 (HER-2), estrogen receptor (PR), and progesterone receptor (PR), may be related to the tumor grade of breast carcinomas [8,9]. A higher tumor grade leads to more aggressive breast carcinomas and poor survival, likely due to hormone receptor negativity, HER-2 positivity, and a larger tumor size of breast carcinomas [10,11]. In addition to the pathologic characteristics of breast tumors, host factors, such as age, race/ethnicity, menopausal status, and parity, may also correlate with tumor grade and influence the aggressive characteristics of breast carcinomas [8,12–15]. However, Somasegar et al. [16] reported that reproductive factors, such as the number of pregnancies, number of births, and age at first period, were not associated with tumor grade. Given that breast cancer is a clinically and genetically heterogeneous disease, traditional clinicopathologic factors were no longer sufficient to evaluate the tumor biology of the general Chinese population, especially for patients in the less developed region of Western China. The identification of the risk factors associated with tumor grade is restricted by the absence of data on large populations in Western China.

Previous studies on specific subtypes of breast carcinoma suggest that the clinicopathologic features of Chinese patients might be distinct from the typical features of breast carcinomas in developed countries [17,18]. However, the potential association between clinicopathologic characteristics (such as menopausal status, ER, PR, HER-2, and tumor size) and the histological tumor grade of breast cancer patients in Western

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Table 1. Clinical Variables and Reproductive Factors of Breast Cancer Patients

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Age at diagnosis (years)							
Mean ± SD	50.2 ± 11.0		50.3 ± 11.1		49.7 ± 10.8		**.0217** *
Range	17-95		19-95		17-89		
≤40	1593	18.48	1161	17.85	432	20.43	**.0066** †
41-45	1601	18.58	1245	19.14	356	16.83	
46-50	1644	19.07	1243	19.11	401	18.96	
51-55	1231	14.28	912	14.02	319	15.08	
56-60	1097	12.73	815	12.53	282	13.33	
≥61	1453	16.86	1128	17.34	325	15.37	
Race/ethnicity							**.0042** †
Han	8288	96.16	6278	96.53	2010	95.04	
Uighur	97	1.13	65	1.00	32	1.51	
Hui	95	1.10	62	0.95	33	1.56	
Zang	27	0.31	15	0.23	12	0.57	
Others	112	1.30	84	1.29	28	1.32	
Method of breast tumor discovery							**<.0001** †
Symptoms	2135	24.77	1656	25.46	479	22.65	
Screening	35	0.41	32	0.49	3	0.14	
Physical examination	439	5.09	360	5.54	79	3.74	
Self-examination	5760	66.83	4242	65.22	1518	71.77	
Others	242	2.81	209	3.21	33	1.56	
Missing data	8	0.09	5	0.08	3	0.14	
Age at menarche (years)							**.0261** †
≤10	21	0.24	18	0.28	3	0.14	
11-12	1074	12.46	840	12.92	234	11.06	
13-14	83	51.37	3362	51.69	106	50.40	
15-16	2229	25.86	1652	25.40	577	27.28	
17-18	716	8.31	516	7.93	200	9.46	
≥19	135	1.57	102	1.57	33	1.56	
Missing data	16	0.19	14	0.22	2	0.09	
Age at menopause							.3946 †
≤40	152	1.76	117	1.80	35	1.65	
41-45	492	5.71	357	5.49	135	6.38	
46-50	1998	23.18	1498	23.03	500	23.64	
51-55	1063	12.83	819	12.59	244	11.54	
56-60	87	1.01	66	1.01	21	0.99	
Missing data	4827	56.00	3647	56.07	1180	55.79	
Marital status							.2219 †
Married	8408	97.55	6334	97.39	2074	98.06	
Never married/Single	64	0.74	50	0.77	14	0.66	
Divorced/Widowed	140	1.62	114	1.75	26	1.23	
Missing data	7	0.08	6	0.09	1	0.05	
Menopausal status							**.0343** †
Premenopausal	4050	46.99	2968	45.63	1082	51.16	
Postmenopausal	3888	45.11	2930	45.05	958	45.30	
Missing data	681	7.90	606	9.32	75	3.55	
Age at first birth (years)							
Mean ± SD	24.25 ± 3.08		24.26 ± 3.06		24.23 ± 3.14		.8101 *
Range	16-48		16-48		17-43		
≤20	236	2.74	178	2.74	58	2.74	.6425 ‡
21-25	1495	17.35	1121	17.24	374	17.68	
26-30	683	7.92	527	8.10	156	7.38	
31-35	55	0.64	39	0.60	16	0.76	
36-40	11	0.13	8	0.12	3	0.14	
≥41	2	0.02	1	0.02	1	0.05	
Missing data	6137	71.20	4630	71.19	1507	71.25	
Number of pregnancies							**<.0001** †
0	2050	23.82	1203	18.50	847	40.05	
1	2639	30.62	2172	33.39	467	22.08	
2	1729	20.06	1394	21.43	335	15.84	
3	1035	12.01	806	12.39	229	10.83	
4	597	6.93	470	7.23	127	6.00	
≥5	558	6.47	451	6.93	107	5.06	
Missing data	11	0.13	8	0.12	3	0.14	
Number of births							**<.0001** †
0	1854	21.51	1124	17.28	730	34.52	
1	4018	46.62	3283	50.48	735	34.75	
2	1806	20.95	1406	21.62	400	18.91	

(continued on next page)

TABLE 1 (*continued*)

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
3	588	6.82	427	6.57	161	7.61	
4	223	2.59	165	2.54	58	2.74	
≥5	123	1.43	93	1.43	30	1.42	
Missing data	7	0.08	6	0.09	1	0.05	
Breast feeding history							.0694 †
Yes	2625	30.46	2052	31.55	573	27.09	
No	212	2.46	177	2.72	35	1.65	
Missing data	5782	67.08	4275	65.73	1507	71.25	

* Student's *t* test.
† Chi-square test.
‡ Fisher's exact test.

China is still not clear. The purpose of current study was to investigate whether epidemiological and clinicopathologic characteristics were associated with the histological tumor grade of female breast cancer patients in Western China.

Patients and Methods

Study Population and Data Collection

The current study was a multicenter joint study conducted by the Western China Clinical Cooperation Group (WCCCG). Cases of breast cancer diagnosed between January 1, 2006, and April 30, 2017, were selected from the WCCCG database, including 23 breast cancer centers in 9 provinces in Western China (i.e., Ganshu, Ningxia, Xinjiang, Chongqing, Sichuan, Yunnan, Guizhou, Shaanxi, and Guangxi). This study was approved by the relevant Institutional Review Boards of each center. Data from the WCCCG were extracted from the clinical medical records of breast cancer patients. This database contains the clinicopathologic information and treatment characteristics of nearly 19,000 breast cancer patients. Patients were excluded if they did not have pathology reports, if they did not have records on their histological tumor grade, if they had a high amount of missing data related to clinicopathologic and treatment characteristics, if the patients were younger than 16 years or older than 100 years of age, or if they were male breast cancer patients. Finally, a total of 8619 female breast cancer patients were included in this study. Eligible patients were categorized into two groups according to their histological tumor grade: Group I (tumor grade I and tumor grade II) with 6504 patients and Group II (tumor grade III) with 2115 patients.

Clinicopathologic Characteristics and Treatment

The WCCCG database provided clinical and reproductive information, such as age at diagnosis, race/ethnicity, age at menarche, age at menopause, marital status, menopausal status, age at first birth, number of pregnancies, number of births, breast feeding history, tumor location, axillary lymph lode status, tumor size, and initial disease symptoms and signs. Treatment characteristics and imaging tests were also extracted from the database. Four common initial disease symptoms and signs were evaluated, including breast lumps, breast pain, nipple discharge, and nipple inversion.

Histological tumor grade was evaluated by the Nottingham grading system and described by the following categories: grade I, grade II, and grade III. These grades were obtained from the database from the short summary of the pathology report. Pathological factors, such as tumor grade, tumor histology, positive axillary lymph nodes, lymphovascular invasion, P53, Ki67, ER/PR/HER-2 status, and histological types of invasive breast carcinoma, were abstracted from the pathology results in patients' medical records.

The cutoff for PR positivity and ER positivity was >3% positive tumor cells with nuclear staining. Tumors were subsequently categorized into four ER/PR subgroups according to their joint ER/PR status: ER+/PR+, ER−/PR−, ER+/PR−, and ER−/PR+. HER-2 status was determined by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH). HER-2 positivity was either IHC 3+ or FISH amplified. Tumors with no (0) or weak (1+) staining were considered HER-2 negative, while tumors with strong (3+) staining were defined as HER-2 positive. FISH was used to confirm HER-2 status if IHC staining yielded 2+ results. If IHC staining was 2+ but FISH was positive, the tumors were considered HER-2 positive. If IHC staining was 2+ and FISH was negative, the tumors were classified as HER-2 negative. If IHC staining was 2+ and FISH was missing, the tumors were classified as borderline. Triple-negative subtype was defined as ER negative, PR negative, and HER-2 negative.

Tumor location was determined by the results of ultrasound or magnetic resonance imaging (MRI) of the breast in patients' medical records. Tumor location was classified as follows: lateral location (upper outer quadrant, lower outer quadrant, 3 o'clock of the left breast, and 9 o'clock of the right breast), medial location (upper inner quadrant, lower inner quadrant, 9 o'clock of the left breast, and 3 o'clock of the right breast) and central location (periareolar, 12 o'clock of the breast, and 6 o'clock of the breast).

Five commonly used imaging tests were used, including ultrasound, mammography, computed tomography (CT), MRI, and bone scanning. Additionally, adjuvant systemic treatment was assessed, including adjuvant chemotherapy, radiotherapy, anti–HER-2 therapy, endocrine therapy, types of adjuvant chemotherapy, types of surgery, axillary lymph node dissection, and level of axillary lymph node dissection. The three most common types of adjuvant chemotherapy regimens, including TEC, TAC, and CEF, were selected for analysis.

Statistical Analysis

The associations between histological tumor grade and different clinicopathologic variables were examined using Student's *t* tests, chi-square tests, or Fisher's exact tests. Statistically significant variables ($P < .05$) in univariate analysis were entered into the multivariate analysis

Table 2. Relationships between Clinical Characteristics and Histological Tumor Grade

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Laterality							.1516*
Right	4088	47.43	3110	47.82	978	46.24	
Left	4437	51.48	3316	50.98	1121	53.00	
Bilateral	77	0.89	63	0.97	14	0.66	
Missing data	17	0.20	15	0.23	2	0.09	
Tumor location in breast							.0007*
Lateral	4394	50.98	3323	51.09	1071	50.64	
Medial	1789	20.76	1409	21.66	380	17.97	
Central	966	11.21	700	10.76	266	12.58	
Missing data	1470	17.06	1072	16.48	398	18.82	
Clinical axillary lymph nodal status							<.0001*
Positive	2198	25.50	1545	23.75	653	30.87	
Negative	6364	73.84	4913	75.54	1451	68.61	
Missing data	57	0.66	46	0.71	11	0.52	
Clinical supraclavicular lymph node status							.4205*
Positive	123	1.43	89	1.37	34	1.61	
Negative	8447	98.00	6378	98.06	2069	97.83	
Missing data	49	0.57	37	0.57	12	0.57	
Tumor size (cm)							<.0001*
≤1 cm	347	4.03	288	4.43	59	2.79	
>1, ≤2 cm	2856	33.14	2271	34.92	585	27.66	
>2, ≤5 cm	3603	41.80	2655	40.82	948	44.82	
>5 cm	256	2.97	167	2.57	89	4.21	
Missing data	1557	18.06	1123	17.27	436	20.52	
Primary breast carcinoma							.1810*
Yes	8183	94.94	6253	96.14	1930	91.25	
No	114	1.32	81	1.25	33	1.56	
Missing data	322	3.74	170	2.61	152	7.19	
Distant metastasis							.0140*
Negative	8404	97.51	6349	97.62	2055	97.16	
Positive	54	0.63	33	0.51	21	0.99	
Missing data	161	1.87	122	1.88	39	1.84	

* Chi-square test.

using logistic regression models. Multivariate logistic regression models were performed to estimate ORs and 95% CIs as measures of the relative risk associated with exposure variables. Missing data were excluded from all models estimated. The statistical software SAS (version 9.4, SAS Institute Inc., Cary, NC) was used to perform all analyses. *P* values less than .05 were considered statistically significant.

Results

Relationship between Clinical Variables and Reproductive Factors and Histological Tumor Grade

Clinical variables and reproductive factors of breast cancer patients are shown in Table 1. Of the entire sample of 8619 cases, 6504 cases (75%) were in grade I/II and 2115 cases (25%) were in grade III. The mean age for the entire sample of patients was 50.2 ± 11.0 years (range 17-95 years). Younger patients (≤40 years) were more likely to be in tumor grade III, whereas older patients (≥61 years) were more likely to be in tumor grade I/II (*P* = .0066). With respect to the method of breast tumor discovery, the most common method was breast self-examination. Compared with grade I/II tumors, grade III tumors were more frequently discovered by breast self-examination and were less likely to be discovered through symptoms (*P* < .0001). Although the majority of patients in Group I and Group II were Han, Group II had more minority patients from the Uighur (1.51%), Hui (1.56%), and Zang (0.57%) groups (*P* = .0042). Among the 8619 patients, the most common age of menarche ranged from 13 to 14 years. A later age of menarche (range 15-18 years) was associated with an increased risk of grade III tumors. Compared to those with a later age at menarche (≥15 years), patients with age at menarche (≤14 years) were at a slightly increased risk of grade I/II tumors (*P* = .0261). Compared with postmenopausal patients, premenopausal patients were more likely to have grade III tumors (51.16% vs. 45.63%) (*P* = .0343). Patients who had never given birth were more likely to have grade III tumors, while patients who had given birth one or two times were more likely to have grade I/II tumors (*P* < .0001). Compared to patients who had one or more pregnancies, patients who had never been pregnant were more likely to have an increased risk of grade III tumors (*P* < .0001). With respect to marital status, age at first birth, menopausal age and breastfeeding history, no significant associations were found between Group I and Group II.

Relationship between Clinical Characteristics and Histological Tumor Grade

The probability of a grade III tumor in the right side of the breast was similar to the probability for the left side (*P* = .1516). Patients in Group II were more likely to have a larger tumor size (49.03%) (including >2, ≤5 cm and> 5 cm, *P* < .0001) than patients in Group I. In addition, patients with grade III tumors were more likely to have positive axillary lymph nodes than patients with grade I/II tumors (30.87% vs. 23.75%, *P* < .0001). With regard to distant

metastasis, the proportion of positive distant metastasis was slightly higher in Group II than in Group I (0.99% vs. 0.51%, $P = .0140$). Interestingly, the proportion of patients with a medial tumor was higher in Group I than in Group II (21.66% vs. 17.97%, $P = .0007$), whereas the proportion of patients with a central tumor was lower in the former group than in the latter group (10.76% vs. 12.58%, $P = .0007$). There were no significant differences in laterality, clinical supraclavicular lymph node status and primary breast carcinoma between Group I and Group II (Table 2).

We also evaluated the differences in initial disease symptoms and signs between Group I and Group II (Table 3). The majority of patients in both Group I and Group II presented with complaints of breast lumps. Compared with patients in Group I, patients in Group II were more likely to present with breast lumps (97.45% vs. 95.80%, $P = .0006$) and breast pain (12.39% vs. 10.81%, $P = .0454$). There was no significant difference in nipple discharge ($P = .9274$) and nipple inversion ($P = .7641$) between Group I and Group II.

Relationship between Pathological Characteristics and Histological Tumor Grade

The pathological characteristics of the tumors are shown in Table 4. Group I had more patients receiving tumor biopsies before operation (52.26% vs. 37.64%, $P < .0001$) and sentinel lymph lode biopsies (18.31% vs. 11.91%, $P < .0001$) than Group II. Grade I/II tumors were strongly associated with lymph lode negativity (42.30% vs. 27.61%, $P < .0001$), whereas grade III tumors were significantly associated with at least five positive lymph lodes (5-10: 9.50% vs. 9.23%, $P < .0001$; >10: 28.46% vs. 12.88%, $P < .0001$).

Although the majority of tumors did not present with lymphovascular invasion, grade III tumors were more frequently associated with lymphovascular invasion than grade I/II tumors (2.55% vs. 1.86%, $P < .0001$). Compared with grade I/II tumors, grade III tumors more likely to be ER negative (46.48% vs. 29.47%, $P < .0001$), PR negative (52.96% vs. 37.93%, $P < .0001$), ER–/PR– (42.84% vs. 25.95%, $P < .0001$), and HER-2 positive (16.60% vs. 11.93%, $P < .0001$) and less likely to be ER+/PR+ (41.13% vs. 55.97%, $P < .0001$) and ER+/PR– (10.12% vs. 11.81%, $P = .0285$). ER–/PR+ did not differ significantly between Group I and Group II (3.43% vs. 3.50%, $P = .9045$). Compared with grade I/II tumors, grade III tumors displayed more Ki67 positivity (60.05% vs. 45.11%, $P = .0307$) and triple negativity (21.56% vs. 10.05%, $P < .0001$).

In addition, the histological types of invasive breast carcinoma were also evaluated in Group I and Group II (Table 5). Patients with grade III tumors were somewhat more likely to have invasive ductal carcinoma (84.78% vs. 80.95%, $P < .0001$) and medullary carcinoma (1.56% vs. 0.32%, $P < .0001$).

Imaging Tests for the Breast

Imaging test results performed particularly for the breast are shown in Table 6. For all cases, the majority of patients had received ultrasound and mammography for the breast, and fewer patients had received CT and MRI. The proportion of patients receiving ultrasound (98.00% vs. 95.79%, $P < .0001$), mammography (92.60% vs. 88.65%, $P < .0001$), and MRI (5.15% vs. 3.55%, $P = .0026$) was higher in Group I than in Group II. However, patients in Group II were more likely to receive CT (3.45% vs. 2.60%, $P = .0391$). No significant differences were observed in records of mammograms ($P = .9102$) and bone scanning ($P = .2984$).

Treatment Characteristics of Breast Cancer Patients

Treatment characteristics of breast cancer patients are shown in Table 7. Patients in Group I were more likely to receive endocrine therapy (24.06% vs. 14.56%, $P < .0001$) and less likely to receive adjuvant chemotherapy (86.25% vs. 87.66%, $P = .0098$) and anti–HER-2 therapy (0.95% vs. 1.47%, $P = .0436$). TEC was the most common type of adjuvant chemotherapy and was more frequently performed in Group II than in Group I (24.59% vs. 22.91%, $P < .0001$). However, TAC was more frequently performed in Group I than in Group II (15.96% vs. 10.21%, $P < .0001$). In terms of type of surgery, patients in Group II were more likely to be treated with a mastectomy (88.61% vs. 84.62%, $P < .0001$) and less likely to receive breast reconstruction (0.33% vs. 1.80%, $P < .0001$) and breast-conserving surgery (8.27% vs. 10.75%, $P < .0001$). Regarding the level of axillary lymph node dissection, the proportion of level I/II was higher (69.42% vs. 64.21%, $P = .0015$) and that of level III was lower (13.79% vs. 15.98%, P = .0015) in Group I than in Group II. We did not observe significant differences by radiotherapy, surgery, and axillary lymph node dissection.

Table 3. Initial Disease Symptoms and Signs

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Breast lump							.0006*
Yes	8292	96.21	6231	95.80	2061	97.45	
No	327	3.79	273	4.20	54	2.55	
Breast pain							.0454*
Yes	965	11.2	703	10.81	262	12.39	
No	7654	88.8	5801	89.19	1853	87.61	
Nipple discharge							.9274*
Yes	161	1.87	121	1.86	40	1.89	
No	8458	98.13	6383	98.14	2075	98.11	
Nipple inversion							.7641*
Yes	149	1.73	114	1.75	35	1.65	
No	8470	98.27	6390	98.25	2080	98.35	

* Chi-square test.

Table 4. Relationships between Pathological Characteristics and Histological Tumor Grade

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Tumor biopsy before operation							<.0001*
Yes	4195	48.67	3399	52.26	796	37.64	
No	4346	50.42	3040	46.74	1306	61.75	
Missing data	78	0.90	65	1.00	13	0.61	
No. of positive axillary lymph nodes							<.0001*
0	3335	38.69	2751	42.30	584	27.61	
1	829	9.62	658	10.12	171	8.09	
2	521	6.04	398	6.12	123	5.82	
3	310	3.60	235	3.61	75	3.55	
4	234	2.71	187	2.88	47	2.22	
5-10	801	9.29	600	9.23	201	9.50	
>10	1440	16.71	838	12.88	602	28.46	
Missing data	1149	13.33	837	12.87	312	14.75	
Sentinel lymph node biopsy							<.0001*
Yes	1443	16.74	1191	18.31	252	11.91	
No	6826	79.20	5042	77.52	1784	84.35	
Missing data	350	4.06	271	4.17	79	3.74	
Lymphovascular invasion							<.0001*
Yes	175	39.24	121	1.86	54	2.55	
No	5062	58.73	4150	63.81	912	43.12	
Missing data	3382	39.24	2233	34.33	1149	54.33	
ER status							<.0001*
Positive	5507	63.89	4421	67.97	1086	51.35	
Negative	2900	33.65	1917	29.47	983	46.48	
Missing data	212	2.46	166	2.55	46	2.17	
PR status							<.0001*
Positive	4823	55.96	3875	59.58	948	44.82	
Negative	3587	41.62	2467	37.93	1120	52.96	
Missing data	209	2.42	162	2.49	47	2.22	
ER+/PR+							<.0001*
Yes	4510	52.83	3640	55.97	870	41.13	
No	3873	44.94	2679	41.19	1194	56.45	
Missing data	236	2.74	185	2.84	51	2.41	
ER–/PR–							<.0001*
Yes	2594	30.10	1688	25.95	906	42.84	
No	5789	67.17	4631	71.20	1158	54.75	
Missing data	236	2.74	185	2.84	51	2.41	
ER+/PR–							.0285*
Yes	982	11.39	768	11.81	214	10.12	
No	7401	85.87	5551	85.35	1850	87.47	
Missing data	236	2.74	185	2.84	51	2.41	
ER–/PR+							0.9045*
Yes	297	3.45	223	3.43	74	3.50	
No	8086	93.82	6096	93.73	1990	94.09	
Missing data	236	2.74	185	2.84	51	2.41	
HER-2 status							<.0001*
Positive	1127	13.08	776	11.93	351	16.60	
Negative	4397	51.02	3328	51.17	1069	50.54	
Borderline(IHC++)	2022	23.46	1650	25.37	372	17.59	
Missing data	1073	12.45	750	11.53	323	15.27	
Triple negative							<.0001*
Yes	1175	13.63	719	11.05	456	21.56	
No	6318	73.30	4989	76.71	1329	62.84	
Missing data	1126	13.06	796	12.24	330	15.60	
Ki67							.0127*
Positive	3742	43.42	2934	45.11	808	60.05	
Negative	248	2.88	211	3.24	37	1.75	
Missing data	4629	53.71	3359	51.65	1270	60.05	

Abbreviations: *ER*, estrogen receptor; *PR*, progesterone receptor; *HER-2*, human epidermal growth factor receptor 2.
* Chi-square test.

Suspected Clinicopathologic Risk Factors for Histological Tumor Grade

Multivariate logistic regression analysis was performed to evaluate the clinicopathologic factors associated with the risk of a high tumor grade (Table 8). ER–/PR– [odds ratio (OR) = 1.841; 95% confidence interval (CI): 1.428-2.374], lymphovascular invasion (OR = 1.657; 95% CI: 1.045-2.629), at least 10 of the positive axillary lymph nodes (OR = 1.813; 95% CI: 1.361-2.414), and triple negativity (OR = 1.810; 95% CI: 1.349-2.427) were positively associated with the risk of a high tumor grade. In addition, larger

Table 5. Histological Types of Invasive Breast Carcinoma

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Ductal carcinoma							<.0001*
Yes	7058	81.89	5265	80.95	1793	84.78	
No	1561	18.11	1239	19.05	322	15.22	
Mucinous carcinoma							.2185*
Yes	85	0.99	69	1.06	16	0.76	
No	8534	99.01	6435	98.94	2099	99.24	
Lobular carcinoma							.0716*
Yes	124	1.44	85	1.31	39	1.84	
No	8495	98.56	6419	98.69	2076	98.16	
Medullary carcinoma							<.0001*
Yes	54	0.63	21	0.32	33	1.56	
No	8565	99.37	6483	99.68	2082	98.44	

* Chi-square test.

tumor size also increased the risk of a high tumor grade (>2, ≤5 cm: OR = 1.804, 95% CI: 1.020-3.192; >5 cm: OR = 2.428; 95% CI: 1.163-5.068). Relative to patients who had never been pregnant, patients who had experienced one or more pregnancies had a significantly lower risk of a high tumor grade (1: OR = 0.326; 95% CI: 0.250-0.423; 2: OR = 0.355; 95% CI: 0.265-0.476; 3: OR = 0.436; 95% CI: 0.308-0.617; 4: OR = 0.441; 95% CI: 0.284-0.685; ≥5: OR = 0.221; 95% CI: 0.128-0.379).

Discussion

Western China has some of largest environmental, economic, and health disparities in the nation, and the most obvious of these disparities are associated with poor strategies for the diagnosis and treatment of cancer patients. Breast cancer patients in Western China are an important population that is still understudied compared with patients in developed regions. In this retrospective epidemiological study, we collected information on 8619 female breast cancer patients, which make this study the largest multicenter program related to histological tumor grades.

Although screening mammography is widely considered the gold standard for the early detection of breast cancer in high-income countries, it is not routinely used for women in Western China because of their low socioeconomic circumstances [19,20]. We observed that the majority of patients discovered breast tumors by accident. Patients in Group II more frequently discovered tumors by self-examination, which might be due to a larger tumor size (>2 cm). Interestingly, we observed that high-grade tumors tended to present with a central tumor location, whereas low-grade tumors tended to present with lateral and medial tumor locations, findings that have not been previously reported.

Table 6. Imaging Tests for Breast

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Ultrasound							<.0001*
Yes	8400	97.46	6374	98.00	2026	95.79	
No	219	2.54	130	2.00		4.21	
Mammography							<.0001*
Yes	7898	91.63	6023	92.60	1875	88.65	
No	721	8.37	481	7.40	240	11.35	
Record of mammogram							.9102*
Malignant calcification	318	3.69	254	3.91	64	3.03	
Mass	2788	32.35	2204	33.89	584	27.61	
Mass combined with calcification	1988	23.07	1567	24.09	421	19.91	
Missing data	3525	40.90	2479	38.12	1046	49.46	
CT							.0391*
Yes	242	2.81	169	2.60	73	3.45	
No	8337	97.19	6335	97.40	2042	96.55	
MRI							.0026*
Yes	410	4.76	335	5.15	75	3.55	
No	8209	95.24	6169	94.85	2040	96.45	
Bone scanning							.2984*
Yes	673	7.81	519	7.98	154	7.28	
No	7946	92.19	5985	92.02	1961	92.72	

Abbreviations: *CT*, computed tomography; *MRI*, magnetic resonance imaging.
* Chi-square test.

Table 7. Treatment Characteristics of Breast Cancer Patients

Characteristics	Total		Group I (I/II)		Group II (III)		*P* Value
	(*N* = 8619)		(*N* = 6504)		(*N* = 2115)		
	n	%	*n*	%	*n*	%	
Adjuvant chemotherapy							.0098*
Yes	7464	86.60	5610	86.25	1854	87.66	
No	991	11.50	782	12.02	209	9.88	
Missing data	164	1.90	112	1.72	52	2.46	
Radiotherapy							.1022*
Yes	1287	15.25	950	14.61	337	15.93	
No	7153	82.99	5432	83.52	1721	81.37	
Missing data	179	2.08	122	1.88	57	2.70	
Anti-HER2 therapy							.0436*
Yes	93	1.98	62	0.95	31	1.47	
No	8355	96.94	6325	97.25	2030	95.98	
Missing data	171	1.98	117	1.80	54	2.55	
Endocrine therapy							<.0001*
Yes	1873	21.73	1565	24.06	308	14.56	
No	6565	76.17	4816	74.05	1749	82.70	
Missing data	181	2.10	123	1.89	58	2.74	
Types of adjuvant chemotherapy							<.0001*
TEC	2010	23.32	1490	22.91	520	24.59	
TAC	1254	14.55	1038	15.96	216	10.21	
CEF	672	7.80	495	7.61	177	8.37	
Others	3363	39.02	2473	38.02	890	42.08	
Missing data	1320	15.32	1008	15.50	312	14.75	
Surgery							.0648*
Yes	8010	92.93	6046	92.96	1964	92.86	
No	30	0.35	27	0.42	3	0.14	
Missing data	579	6.72	431	6.63	148	7.00	
Type of surgery							<.0001*
Mastectomy	7378	85.60	5504	84.62	1874	88.61	
Breast reconstruction	124	1.44	117	1.80	7	0.33	
Breast-conserving surgery	874	10.14	699	10.75	175	8.27	
Others	65	0.75	53	0.81	12	0.57	
Missing data	178	2.07	131	2.01	47	2.22	
Axillary lymph node dissection							.3498*
Yes	7572	87.85	5715	87.87	1857	87.80	
No	820	9.51	631	9.70	189	8.94	
Missing data	227	2.63	158	2.43	69	3.26	
Level of axillary lymph node dissection							.0015*
I, II	5873	68.14	4515	69.42	1358	64.21	
III	1235	14.33	897	13.79	338	15.98	
Missing data	1511	17.53	1092	16.79	419	19.81	

* Chi-square test.

The present study, similar to other previous studies [21,22], showed a significantly higher proportion of grade III tumors in patients ≤40 years of age. Given the lack of routine screening mammography guidelines for women ≤40 years of age in Western China, it is possible that these patients more frequently present with a palpable mass and that their tumors tend to be larger and have more axillary lymph node involvement than breast cancers detected by screening. In addition, our results showed that patients who presented with high-grade tumors were more likely to be positive for pathological lymphovascular invasion and distant metastasis. These data may directly indicate that high-grade tumors of breast cancer have more aggressive behavior and poorer prognosis in patients in Western China.

In this multiethnic study in Western China, in which nearly 97% of the sample were Han, significant racial disparities were found for different tumor grades. The minorities (Uighur, Hui, and Zang) were more likely to present with grade III tumors than Han. It is possible that minority races in Western China have different lifestyles and a less developed awareness of health issues. Taking into consideration that minorities in Western China have higher tumor grades, interventions are needed that provide socioeconomic and health-related support that enables minorities to detect breast carcinomas in their early stages.

Previous studies have shown that reproductive factors, such as parity, number of pregnancies, age at menarche, and age at first birth, were related to the risk of breast cancer subtypes [23,24], but the association between these variables and tumor grade was still controversial [13,16]. In the current study, we investigated the influence of reproductive factors, such as the number of births, number of pregnancies, and age at menarche, on tumor grade. We found that reproductive factors affected the histological tumor grade of breast cancer differently. For example, patients with an earlier age at menarche (≤12 years) were more likely to be diagnosed with grade I/II tumors, whereas patients with a later age at menarche (15-18 years) were more likely to be diagnosed with grade III tumors. We further found that premenopausal patients were at a significantly increased risk of high tumor grades. Breast cancer is most common among postmenopausal patients; however, the number of premenopausal patients with breast cancers is increasing around the world [25–27]. Postmenopausal status is associated with decreased levels of progesterone and estrogen and was hypothesized to be

Table 8. Adjusted ORs and 95% CIs for the Association between Suspected Clinicopathologic Risk Factors and Risk of Histological Tumor Grade

Factors	*P* Value	OR (95%CI)
Number of pregnancies		
0 *		
1	<.0001	0.326(0.250-0.423)
2	<.0001	0.355(0.265-0.476)
3	<.0001	0.436(0.308-0.617)
4	.0003	0.441(0.284-0.685)
≥5	<.0001	0.221(0.128-0.379)
Tumor size (cm)		
≤1 cm *		
>1, ≤2 cm	.2108	1.446(0.812-2.575)
>2, ≤5 cm	.0427	1.804(1.020-3.192)
>5 cm	.0182	2.428(1.163-5.068)
No. of positive axillary lymph nodes		
0 *		
1	.1859	1.242(0.901-1.711)
2	.2542	1.232(0.860-1.765)
3	.6689	0.890(0.523-1.516)
4	.4113	1.247(0.736-2.113)
5-10	.2676	1.203(0.868-1.668)
>10	<.0001	1.813(1.361-2.414)
Lymphovascular invasion		
No *		
Yes	.0318	1.657(1.045-2.629)
ER–/PR–		
No *		
Yes	<.0001	1.841(1.428-2.374)
Triple negative		
No *		
Yes	<.0001	1.810(1.349-2.427)

Nonsignificant ($P > .05$) data were not listed.
* Referent.

associated with low tumor grade and less aggressive tumors. Taken together, these results suggest that premenopausal patients may be more likely to have elevated exposure to estrogen or progesterone, which may influence the aggressive behavior of breast cancer in patients in Western China. We also observed that parity was a protective factor and was associated with a decreased risk of high tumor grade. The number of pregnancies and number of births were inversely associated with the risk of high tumor grade. Compared with parous patients with one or more births/pregnancies, nulliparous patients were more likely to be diagnosed with high-grade tumors. Based on these results, the fact that reproductive factors, including age at menarche, number of pregnancies, number of births, and menopausal status, were all associated with a risk of high tumor grade provides possible evidence that these reproductive factors may influence the risk of breast cancer through hormonal mechanisms. There were other potential mediators, including hormonal and lifestyle risk factors (such as education, cigarette smoking, alcohol consumption, and oral contraceptives) that might affect tumor grade. Because data on these factors were not collected in our database, we were unable to investigate their contribution to the association between clinical factors and tumor grade in current study.

We found that high-grade tumors were significantly associated with large tumor size (>2 cm) and clinicopathologic positive axillary lymph nodes (especially >5 lymph nodes), which supported findings from previous studies [7,28]. Previous studies have shown that high-grade tumors were significantly associated with hormone receptor negativity [29] and HER-2 positivity [30] in breast cancer patients. Consistent with these studies, our study has shown that ER-negative or PR-negative tumors were strongly associated with an increased risk of a high tumor grade. In addition, we expanded the analysis of hormone receptors and further evaluated the association between joint ER/PR status and tumor grade. We observed that ER+/PR+ and ER+/PR– tumors had a decreased risk of a high tumor grade, whereas ER–/PR– tumors had an increased risk of a high tumor grade. Furthermore, we found that tumors with HER-2 or Ki67 positivity and triple negativity had an increased risk of a high tumor grade. Taken together, these results suggest that the abovementioned pathological factors might affect the tumor grade and ultimately cause more aggressive breast cancer among breast cancer patients in Western China. Although medullary carcinomas are rare, we observed that medullary carcinomas tend to be high grade. This finding was similar to those of previous studies showing that breast cancer patients presenting with medullary carcinomas showed a poorer grade than patients with other histological subtype carcinomas [31,32].

In the present study, tumor grade was also associated with different treatment patterns, and patients with high-grade tumors appeared to receive more aggressive treatments, such as adjuvant chemotherapy, anti–HER-2 therapy, mastectomy, and level III axillary lymph lode dissection. However, patients with low-grade tumors tended to receive endocrine therapy, breast reconstruction, breast-conserving surgery, and level I/II axillary lymph lode dissection. This finding might be explained by the fact that high-grade tumors were more likely to be large in size, HER-2 positive, and hormone receptor negative and to have positive axillary lymph nodal status.

To the best of our knowledge, to date, there have been no studies that have investigated the relationship between clinicopathologic factors and the histological tumor grades of breast cancer patients in Western China. The identification of factors associated with the histological tumor grade of breast cancer is hampered by the absence of data on large populations in Western China. The main strength of our study is that our study population was large and spanned many centers in Western China, in contrast to previous reports performed within single institutions or geographic regions.

The present study also has potential limitations, including a retrospective design using a database from the WCCCG. First, because follow-up data were not available in our database, we were unable to address the question of whether a high tumor grade was associated with the poor prognosis of breast cancer patients in Western China. Further studies are needed to assess the true association between histological tumor grade and the prognosis of breast cancer patients in Western China. Second, mammography screening is not routinely performed for women in Western China, and we are unable to obtain data regarding mammography screening program participation. Therefore, we cannot assess whether mammography screening programs could decrease the risk of high tumor grades. Third, pathological variables, such as ER, PR, HER-2, P53, and Ki67 status, were not assessed centrally since the data were abstracted from clinical medical records. Several patients did not have available data on the pathological details of lymphovascular invasion and P53 and Ki67 status because these were not routinely recorded in earlier pathology reports in Western China. Finally, there was also a large amount of missing data regarding age at first birth and breastfeeding history. Therefore, it is possible that the true association between these clinicopathologic variables and the histological tumor grade of breast cancer patients in Western China was not fully elucidated. In addition, data on several of the lifestyle and reproductive risk factors that we did not collect may also influence the histological tumor grade of breast cancer.

Conclusion

Our results support the hypothesis that clinicopathologic factors have different influences on histological tumor grade and highlight the need to identify specific risk factors for the tumor grade of breast cancer among patients in Western China. In the current study, it was reasonable to speculate that the events associated with increases in estrogen/progesterone levels in young and premenopausal patients may influence the progression of breast tumors, resulting in more rapid growth of tumors that present with large size, high grade, axillary lymph nodes metastasis, and lymphovascular invasion and ultimately lead to distant metastasis and poorer prognosis.

Routine screening mammography is not currently performed due to the less developed socioeconomic background in Western China, which is possibly one of the factors leading to a greater number of later-stage tumors characterized as high-grade and large in size. Our results indicated that patients who had never been pregnant or given birth were at a high risk of high-grade tumors. Although there were still no final conclusions about the role of reproductive factors in histological tumor grade, we suggested that these patients should be given more attention. Positive axillary lymph nodes, large tumor size (>2 cm), lymphovascular invasion, ER negativity/PR negativity, and triple negativity were risk factors for high tumor grades in breast cancer patients in Western China.

Taken together, our results support the hypothesis that breast cancer patients with high-grade tumors may be clinically and biologically distinct from breast cancer patients with low-grade tumors in Western China.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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