Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(8) 1–15
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0300060520949041
journals.sagepub.com/home/imr
SAGE

Association between body mass index and clinical characteristics, as well as with management, in Chinese patients with breast cancer

Bin Wang[1,*], Lizhe Zhu[1,*], Siyuan Jiang[1], Lizhi Zhao[2], Yuhui Zhou[1], Ligang Niu[1], Yu Yan[1] and Ke Wang[1]

Abstract

Objective: Body mass index (BMI) is a risk factor associated with breast cancer in postmenopausal women. This study aimed to identify the associations of BMI with clinical characteristics and management of breast cancer in female Chinese patients.

Methods: Clinicopathological information on 1296 women who were diagnosed with breast cancer was collected at our hospital. We recorded the clinicopathological characteristics, molecular phenotypes, manner of diagnosis, implementation rate of preoperative examinations, and surgical method used.

Results: Significant differences were found in the tumor size, disease stage, manner of diagnosis, implementation rate of preoperative examinations, and the surgical method among different BMI groups. In premenopausal patients, significant differences were found in the distribution of molecular phenotypes and surgical approach among different BMI groups. In postmenopausal patients, different BMI groups showed significant differences in the tumor size, disease stage, distribution of molecular phenotypes, manner of diagnosis, rate of implementation of preoperative mammography, and surgical method.

Conclusion: Higher BMI is associated with a larger tumor size, more advanced disease stage, diagnosis by physical examination, higher implementation rate of preoperative examinations, and lower radical surgery rate in Chinese women with breast cancer. However, the relationship between BMI and molecular phenotypes differs between pre- and postmenopausal women.

[1]Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China
[2]Department of Oncosurgery, Hanzhong Central Hospital, Hanzhong, Shaanxi Province, China

*These authors contributed equally to this work.

Corresponding author:
Ke Wang, Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta Western Road, Xi'an, Shaanxi Province 710061, China.
Email: 979915080@qq.com

Keywords
Breast cancer, body mass index, molecular phenotype, tumor size, menopausal, mammography

Date received: 15 March 2020; accepted: 21 July 2020

Introduction

Currently, breast cancer is one of the most common malignant tumors in women. In recent decades, the incidence of breast cancer has been showing a rising trend worldwide,[1] especially in the Asian region.[2] The incidence of breast cancer was increased by 38.5% and the number of breast cancer-related deaths was 13,000 in China in 2005.[3] Epidemiological studies have shown that the increase in the incidence of breast cancer is associated with changes in various breast cancer-related risk factors, and body mass index (BMI) is an important factor.[4] Furthermore, a number of clinical studies have indicated that BMI is an important risk factor associated with breast cancer in postmenopausal women.[5]

Some researchers have shown that there are certain differences in the effect of BMI in Western and Asian populations.[6] The CBCS and Washington state studies showed that, in postmenopausal women, BMI increased the risk for luminal A and basal-like breast cancer.[7] However, in Japanese postmenopausal patients, the correlation between increased BMI and the risk of breast cancer was limited to patients with estrogen receptor-positive (ER+) breast cancer, and there was no correlation with triple-negative (TN) or basal-like breast cancer.[8] This difference might be related to many factors, including regional differences, ethnic background, living habits, diet structure, the level of economic development, and the education level among others.[9]

This study aimed to study the effects of BMI on the clinicopathological characteristics, implementation rate of preoperative clinical examinations, and surgical approach in Chinese female patients with breast cancer in the Shaanxi area. Hopefully, the results of our study may reflect to a certain extent the trend in breast cancer in other developing countries. Therefore, our findings could help other developing countries to formulate prevention strategies for breast cancer that cater to a developing economy.

Methods

Patients

This retrospective study included female patients with pathologically confirmed primary breast cancer from the First Affiliated Hospital of Xi'an Jiaotong University between February 2016 and January 2019. This hospital is representative of the local Shaanxi area, which is undergoing rapid economic development.[10] All of the cases were reviewed and the patients' information was collected using a case report form. All of the patients enrolled in this study met two main inclusion criteria as follows: (1) pathologically confirmed primary breast cancer and (2) previous treatment (surgery) for breast cancer. The exclusion criterion was distant metastasis at diagnosis.

According to the conventions of the World Health Organization,[11] the enrolled patients were classified into four groups according to their BMI as follows: underweight, BMI < 18.5 kg/m^2; normal weight, BMI $= 18.5$ to 24.99 kg/m^2; overweight, BMI $= 25.0$ to 29.99 kg/m^2; and obese, BMI ≥ 30.0 kg/m^2. BMI was calculated as follows:

$$\text{BMI} = \text{weight(kg)}/\text{height squared(m)}^2$$

Pathological diagnostic criteria

Histological subtype categories were based on the 1981 and 2003 World Health Organization histological classification criteria.[12] Staging of breast cancer was performed according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system of 1997.[13] By convention, TNM stages I and II were classified as early breast cancer, and stage III was regarded as advanced breast cancer.[10]

Immunohistochemistry and molecular typing

The expression levels of ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2), and Ki-67 (cell proliferation marker) in cancer tissue samples were examined using immunohistochemistry by experienced pathologists. ER and PR expression was considered to be positive if $> 1\%$ of the cells showed positive nuclear staining in a single section. The intensity and pattern of Her2 staining in the membrane of tumor cells were evaluated using a scoring system for the categorization of tumors. In brief, the scoring system was as follows: scores of 0 and 1+ (weak immunostaining in $< 30\%$ of the tumor cells) were considered Her2-negative; a score of 2+ (complete, strong membranous staining in at least 10%, but in $< 30\%$, of the tumor cells) was considered as equivocal; and a score of 3+ (uniform intense membranous staining in $\geq 30\%$ of the tumor cells) was considered as Her2-positive. Tumors that were scored 2+ were further assessed by fluorescence *in situ* hybridization (FISH). If positive staining was observed in FISH analysis, tumors with a 2+ score were designated as Her2-positive.[14]

Using the newly recommended method for categorizing breast cancer subtypes,[15] the tumors were grouped into four subtypes as follows: (1) luminal A (ER- and/or PR-positive, Her2-negative, and Ki-67 $< 14\%$); (2) luminal B (ER- and/or PR-positive, Her2-negative, and Ki-67 $\geq 14\%$; or ER- and/or PR-positive, Her2-positive, and any expression of Ki-67); (3) Her2+ (Her2 overexpression, and ER- and PR-negative); and (4) triple-negative ([TN] ER- and PR-negative, Her2-negative, and any expression of Ki-67).

Data collection and quality control

The following data were systematically collected for all enrolled patients via a review of their medical records: (1) general information, including date of diagnosis, visits to other health care professionals, inpatient admission date, diagnosis at admission, and manner of detection; (2) demographic characteristics at the time of diagnosis/admission; (3) data on a clinical breast examination; (4) diagnostic imaging data, including molybdenum target X-ray (mammography) and B-ultrasound data; (5) data on characteristics of the tumor, including primary location of the tumor, primary tumor quadrant, tumor size, tumor invasion, lymph node metastasis, and tumor staging; (6) data on surgical intervention; and (7) data on pathological characteristics, including findings from preoperative cytological and pathological examinations, intraoperative pathological evaluation, postoperative pathological evaluation, and ER, PR, Her-2, and Ki-67 expression.

All patients' information was retrieved from medical records by trained clerks and added to a paper-based case report form. Two data input clerks were recruited for double entry of data from paper to a computer-based database (FoxPro software; FoxPro Inc., Lewiston, PA, USA) independently. All of the complete double-entry databases were validated by running EpiData (The Epidata Association, Odense, Denmark). Any inconsistencies found between the two databases were reported to the clerks for adjudication until both databases were in agreement. As a final check, one of the databases was chosen for a final consistency check. Logistical mistakes were returned to the data collectors, who checked the original medical records and returned a revised database for the final analysis. During the consistency check, 5% of the medical records were randomly selected on the basis of the study ID, and sent for quality control review.

Data analysis

The frequencies of variables related to clinical and pathological characteristics, implementation of the clinical examination, and various treatment patterns were calculated to indicate their distribution in the total population and in different BMI groups. Differences in the distribution of variables among different groups were examined using the chi-square test, the rank-sum test, and Fisher's exact test to obtain P values for the non-association tests. Measurement data are expressed as mean $\pm$ standard deviation. The case-only odds ratio (OR) was used to evaluate the relative strength of the association between BMI and the tumor molecular subtype (i.e., luminal B, Her2+, or TN) versus luminal A, which is the most common subtype.[16]

SPSS statistical software version 22.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Statistical significance was assessed by two-tailed tests with an α level of 0.05.

Ethics

This study was approved by the Medical Ethics Committee of Xi'an Jiaotong University. Patient consent was not required for this study because there were no anticipated risks for the participants. All patient identifiers were removed from the data, according to approved procedures, and the anonymized data were maintained in a secure database that only members of the research team could access. All of the data are reported in aggregate.

Results

General information

Data for 1296 cases were collected, including data on 127 cases in which we were unable to distinguish between luminal A and B types because the level of Ki-67 expression was not detected, 34 cases in which immunohistochemistry showed an Her2 score of 2+, but Her2 expression was not determined with FISH analysis, and 95 cases in which the clinical and pathological information was incomplete. Therefore, 256 cases were excluded, with a final number of cases in this study of 1040.

Table 1. Clinical characteristics and molecular subtypes in the study population.

Characteristics	n	%
Tumor size		
$\leq$2 cm	391	37.6
2–5 cm	553	53.2
>5 cm	96	9.2
Axillary lymph nodes		
Negative	531	51.1
Positive	509	48.9
TNM stage		
Early (I + II)	465	44.7
Advanced (III)	575	55.3
Pathological diagnosis		
Ductal carcinoma	849	81.6
Lobular carcinoma	93	8.9
Others	98	9.4
Tumor site		
Left	535	51.4
Right	505	48.6
Molecular subtype		
Luminal A	529	50.9
Luminal B	177	17.0
Her2+	111	10.7
TN	223	21.4
BMI group		
UW	66	6.3
NW	642	61.7
OW	277	26.6
OB	55	5.3

TNM, tumor-node-metastasis; Her2, human epidermal growth factor receptor 2; TN, triple-negative; BMI, body mass index; UW, underweight; NW, normal weight; OW, overweight; OB, obese.

The mean (standard deviation) age of the women was 42 ± 2 years. Basic clinical and pathological information of all of the patients is shown in Table 1. In this study, more than half of the patients had a tumor diameter of 2 to 5 cm. A higher number of patients had advanced breast cancer than early stage cancer. The main pathological pattern was invasive ductal carcinoma. The most common molecular subtype was luminal A (> 50%), followed by the TN type, and the Her2+ type was the least common. Finally, based on the BMI, > 60% patients were assigned to the normal weight group, while the underweight and obese groups contained only approximately 5% of patients in each group.

Comparison of the clinical and pathological features of breast cancer among the different BMI groups

There were significant differences in the clinical and pathological features of the different BMI groups. With regard to tumor size, in the underweight group, 50% of the patients had a tumor diameter $\leq$2 cm, and the percentage of patients with a tumor diameter $\leq$2 cm gradually decreased with an increase in BMI. Therefore, the tumor diameter significantly increased with an increase in BMI ($P < 0.01$). Similar to the trend in tumor size, the proportion of patients with early-stage breast cancer gradually decreased with an increase in BMI, while the proportion of patients with advanced stage breast cancer gradually increased ($P = 0.04$). There were no significant differences in the other pathological features (axillary lymph node status, pathological diagnosis, tumor site, and molecular type) among the BMI groups (Table 2).

Effect of BMI on the manner of detection of breast cancer and the implementation rate of preoperative examinations

Differences in social factors affect the distribution of BMI in the population, and this difference might also have an effect on the manner of detection and implementation of the preoperative examination. With an

Table 2. Comparison of clinical and pathological features of breast cancer among the different body mass index groups.

Characteristics	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
	66	642	277	55	1040
Tumor size					
$\leq$2 cm	33 (50.0)	236 (36.8)	111 (40.1)	11 (20.0)	391 (37.6)
2–5 cm	28 (42.4)	359 (55.9)	128 (46.2)	38 (69.1)	553 (53.2)
>5 cm	5 (7.6)	47 (7.3)	38 (13.7)	6 (10.9)	96 (9.2)
P value					<0.01**
Axillary lymph nodes					
Negative	38 (57.6)	329 (51.2)	140 (50.5)	24 (43.6)	531 (51.1)
Positive	28 (42.4)	313 (48.8)	137 (49.5)	31 (56.4)	509 (48.9)
P value					0.499*
TNM stage					
Early (I + II)	31 (47.0)	307 (47.8)	105 (37.9)	22 (40.0)	465 (44.7)
Advanced (III)	35 (53.0)	335 (52.2)	172 (62.1)	33 (60.0)	575 (55.3)
P value					0.04**
Pathological diagnosis					
Ductal carcinoma	53 (80.3)	529 (82.4)	221 (79.8)	46 (83.6)	849 (81.6)
Lobular carcinoma	7 (10.6)	54 (8.4)	27 (9.7)	5 (9.1)	93 (8.9)
Others	6 (9.1)	59 (9.2)	29 (10.5)	4 (7.3)	98 (9.4)
P value					0.955***
Tumor site					
Left	32 (48.5)	339 (52.8)	136 (49.1)	28 (50.9)	535 (51.4)
Right	34 (51.5)	303 (47.2)	141 (50.9)	27 (49.1)	505 (48.6)
P value					0.724*
Molecular subtype					
Luminal A	34 (51.5)	322 (50.2)	143 (51.6)	30 (54.5)	529 (50.9)
Luminal B	9 (13.6)	118 (18.4)	42 (15.2)	8 (14.5)	177 (17.0)
Her2+	7 (10.6)	74 (11.5)	26 (9.4)	4 (7.3)	111 (10.7)
TN	16 (24.2)	128 (19.9)	66 (23.8)	13 (23.6)	223 (21.4)
P value					0.799*

UW, underweight; NW, normal weight; OW, overweight; OB, obese; TNM, tumor-node-metastasis; Her2, human epidermal growth factor receptor 2; TN, triple-negative. *Chi-square test; **rank-sum test; ***Fisher's exact test.

increase in BMI, the proportion of patients in whom breast cancer was detected by a physical examination and by accident gradually increased, while the proportion in which it was detected on the basis of symptoms decreased ($P = 0.002$) (Table 3). With regard to preoperative examinations, the overall implementation rate for mammography was much lower than the average rate in developed Western countries. The implementation rate of B-ultrasound was significantly higher than that of mammography ($P < 0.01$). The implementation rate of these two most commonly used preoperative techniques showed the same trend. With an increase in BMI, the implementation rate of mammography gradually increased ($P = 0.06$), as did the implementation rate of B-ultrasound ($P < 0.01$).

Table 3. Effect of body mass index on the manner of detection and the implementation rate of preoperative examinations.

Characteristics	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
	66	642	277	55	1040
Detection					
Physical examination	2 (3.0)	40 (6.2)	22 (7.9)	7 (12.7)	71 (6.8)
Accidental	33 (50.0)	422 (65.7)	193 (69.7)	30 (54.5)	678 (65.2)
Symptom based	31 (47.0)	180 (28.1)	62 (22.4)	18 (32.7)	291 (28.0)
P value					0.002***
Molybdenum target X-ray					
Used	9 (13.6)	124 (19.3)	65 (23.5)	21 (38.2)	219 (21.1)
Not used	52 (78.8)	501 (78.0)	204 (73.6)	32 (58.2)	789 (75.9)
Not clear	5 (7.6)	17 (2.6)	8 (2.9)	2 (3.6)	32 (3.1)
P value					0.06***
B-ultrasound					
Used	49 (74.2)	501 (78.0)	217 (78.3)	36 (65.5)	803 (77.2)
Not used	17 (25.8)	129 (20.1)	55 (19.9)	16 (29.1)	217 (20.9)
Not clear	0 (0.0)	12 (1.9)	5 (1.8)	3 (5.5)	20 (1.9)
P value					0.01*

UW, underweight; NW, normal weight; OW, overweight; OB, obese. *Chi-square test; ***Fisher's exact test.

Table 4. Effect of body mass index on the surgical approach.

Surgical approach	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
	66	642	277	55	1040
Radical mastectomy	0 (0.0)	17 (2.6)	14 (5.1)	3 (5.5)	34 (3.3)
Modified radical mastectomy	60 (90.9)	592 (92.2)	223 (80.5)	39 (70.9)	914 (87.9)
Simple mastectomy + SLNB	5 (7.6)	26 (4.0)	26 (9.4)	9 (16.4)	66 (6.3)
Breast-conserving surgery	1 (1.5)	7 (1.1)	14 (5.1)	4 (7.3)	26 (2.5)
P value					0.01*

UW, underweight; NW, normal weight; OW, overweight; OB, obese; SLNB, sentinel lymph node biopsy. *Chi-square test.

Effect of BMI on the surgical approach

BMI also affected the surgical approach. With an increase in BMI, the implementation rate of radical surgery (modified radical mastectomy) decreased, and the implementation rate of advanced surgical methods (sentinel lymph node biopsy [SLNB] or breast conservation surgery [BCS]) gradually increased ($P < 0.01$) (Table 4).

Effect of BMI on the clinical and pathological features, manner of detection, implementation rate of preoperative examinations, and surgical approach in the premenopausal population

To determine whether BMI is associated with the occurrence of breast cancer in premenopausal and postmenopausal women in

Table 5. Effect of body mass index on the clinical and pathological features, manner of detection, implementation rate of preoperative examinations, and surgical approach in the premenopausal population.

Characteristics	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
	35	292	103	24	454
Molecular subtype					
Luminal A	21 (60.0)	155 (53.1)	49 (47.6)	9 (37.5)	234 (51.5)
Luminal B	6 (17.1)	63 (21.6)	17 (16.5)	2 (8.3)	88 (19.4)
Her2+	4 (11.4)	27 (9.2)	13 (12.6)	2 (8.3)	46 (10.1)
TN	4 (11.4)	47 (16.1)	24 (23.3)	11 (45.8)	86 (18.9)
P value					0.003*
Surgical approach					
Radical mastectomy	0 (0.0)	7 (2.4)	5 (4.9)	1 (4.2)	13 (2.9)
Modified radical mastectomy	33 (94.3)	269 (92.1)	81 (78.6)	19 (79.2)	402 (88.5)
Simple mastectomy + SLNB	2 (5.7)	12 (4.1)	11 (10.7)	3 (12.5)	28 (6.2)
Breast conservation surgery	0 (0.0)	4 (1.4)	6 (5.8)	1 (4.2)	11 (2.4)
P value					0.015***

UW, underweight; NW, normal weight; OW, overweight; OB, obese; Her2, human epidermal growth factor receptor 2; TN, triple-negative; SLNB, sentinel lymph node biopsy. *Chi-square test; ***Fisher's exact test.

Table 6. Effect of body mass index on the clinical and pathological features, manner of detection, implementation rate of preoperative examinations, and surgical approach in the postmenopausal population.

Characteristics	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
	31	350	174	31	586
Tumor size					
≤2 cm	13 (41.9)	112 (32.0)	69 (39.7)	1 (3.2)	195 (33.3)
2–5 cm	16 (51.6)	213 (60.9)	82 (47.1)	28 (90.3)	339 (57.8)
>5 cm	2 (6.5)	25 (7.1)	23 (13.2)	2 (6.5)	52 (8.9)
P value					0.021**
TNM stage					
Early (I + II)	13 (41.9)	158 (45.1)	51 (29.3)	11 (35.5)	233 (39.8)
Advanced (III)	18 (58.1)	192 (54.9)	123 (70.7)	20 (64.5)	353 (60.2)
P value					0.006**
Molecular subtype					
Luminal A	13 (41.9)	167 (47.7)	94 (54.0)	21 (67.7)	295 (50.3)
Luminal B	3 (9.7)	55 (15.7)	25 (14.4)	6 (19.4)	89 (15.2)
Her2 +	3 (9.7)	47 (13.4)	13 (7.5)	2 (6.5)	65 (11.1)
TN	12 (38.7)	81 (23.1)	42 (24.1)	2 (6.5)	137 (23.4)
P value					0.049*
Detection					
Physical examination	0 (0.0)	19 (5.4)	15 (8.6)	5 (16.1)	39 (6.7)
Accidental	10 (32.3)	237 (67.7)	121 (69.5)	16 (51.6)	384 (65.5)
Symptom based	21 (67.7)	94 (26.9)	38 (21.8)	10 (32.3)	163 (27.8)
P value					<0.01***

(continued)

Table 6. Continued.

Characteristics	UW n (%)	NW n (%)	OW n (%)	OB n (%)	Subtotal n (%)
Molybdenum target X-ray					
Used	4 (12.9)	62 (17.7)	42 (24.1)	15 (48.4)	123 (21.0)
Not used	23 (74.2)	280 (80.0)	127 (73.0)	14 (45.2)	444 (75.8)
Not clear	4 (12.9)	8 (2.3)	5 (2.9)	2 (6.5)	19 (3.2)
P value					<0.01***
Surgical approach					
Radical mastectomy	0 (0.0)	10 (2.9)	9 (5.2)	2 (6.5)	21 (3.6)
Modified radical mastectomy	27 (87.1)	323 (92.3)	142 (81.6)	20 (64.5)	512 (87.4)
Simple mastectomy + SLNB	3 (9.7)	14 (4.0)	15 (8.6)	6 (19.4)	38 (6.5)
Breast conservation surgery	1 (3.2)	3 (0.9)	8 (4.6)	3 (9.7)	15 (2.6)
P value					<0.01***

UW, underweight; NW, normal weight; OW, overweight; OB, obese; TNM, tumor-node-metastasis; Her2, human epidermal growth factor receptor 2; TN, triple-negative; SLNB, sentinel lymph node biopsy. *Chi-square test; **rank-sum test; ***Fisher's exact test.

Table 7. Case-only ORs and 95% CIs from logistic regression models of the associations between breast cancer tumor subtypes and BMI.

BMI	Luminal A comparison	Luminal B			Her2+			TN		
	n	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
UW	34	9	1.00	Reference	7	1.00	Reference	16	1.00	Reference
NW	322	118	1.38	0.65–2.97	74	1.12	0.48–2.62	128	0.85	0.45–1.58
OW	143	42	1.11	0.49–2.50	26	0.88	0.35–2.20	66	0.98	0.51–1.90
OB	30	8	1.01	0.35–2.94	4	0.65	0.17–2.43	13	0.92	0.38–2.22
Subtotal	529	177			111			223		
Premenopausal										
UW	21	6	1.00	Reference	4	1.00	Reference	4	1.00	Reference
NW	155	63	1.42	0.55–3.69	27	0.92	0.29–2.87	47	1.59	0.52–4.87
OW	49	17	1.21	0.42–3.51	13	1.39	0.41–4.77	24	2.57	0.79–8.33
OB	9	2	0.78	0.13–4.62	2	1.17	0.18–7.56	11	6.42**	1.61–25.64
Subtotal	234	88			46			86		
Postmenopausal										
UW	13	3	1.00	Reference	3	1.00	Reference	12	1.00	Reference
NW	167	55	1.43	0.39–5.19	47	1.22	0.33–4.46	81	0.53	0.23–1.20
OW	94	25	1.15	0.31–4.36	13	0.60	0.15–2.39	42	0.48	0.20–1.15
OB	21	6	1.24	0.26–5.83	2	0.41	0.06–2.81	2	0.10**	0.02–0.54
Subtotal	295	89			65			137		

OR, odds ratio; CI, confidence interval; BMI, body mass index; Her2, human epidermal growth factor receptor 2; TN, triple-negative; UW, underweight; NW, normal weight; OW, overweight; OB, obese.

*$P < 0.05$; **$P < 0.01$ vs the UW group.

Reference: luminal A is regarded as the reference as the most common subtype.

the current population, we divided our patients into premenopausal and postmenopausal groups (Table 5). BMI had a significant effect on the molecular subtype and surgical approach in premenopausal women as follows. In the underweight and normal weight groups, the proportion of luminal A type cancer was $> 50\%$, and in the overweight and obese groups, the proportion of patients with the TN type was higher compared with that in the underweight and normal weight groups ($P = 0.003$). In the overweight and obese groups, the proportion of patients who underwent SLNB and BCS was higher than that in the underweight and normal weight groups, while the proportion of patients who underwent radical procedures showed the opposite trend ($P = 0.015$). The other pathological features (tumor size, axillary lymph node status, and staging) and the implementation rate of preoperative examinations showed no significant differences among the BMI groups (data not shown).

Effect of BMI on the clinical and pathological features, manner of detection, implementation rate of preoperative examinations, and surgical approach in the postmenopausal population

BMI had a distinct effect in the postmenopausal populations (Table 6). In postmenopausal women, the proportion of patients with early-stage breast cancer was higher in the underweight and normal weight groups than in the overweight and obese groups ($P = 0.006$). The proportion of patients with a tumor size < 2 cm was slightly higher in the overweight group than in the normal weight group. Moreover, the proportion of patients with a tumor size < 2 cm was higher in the underweight group than in the obese group ($P = 0.021$). Overall, the trend for tumor size and tumor stage was similar. The tumor diameter gradually increased and the tumor stage gradually became more advanced with an increase in BMI. With regard to the molecular phenotype, as BMI increased, the proportion of patients with the luminal A type gradually increased, while the proportion of those with the TN type gradually decreased ($P = 0.049$). The proportion of patients in whom tumors were found by a physical examination or by accident was significantly higher in the obese group than in the underweight group. Similarly, the proportion of such patients was higher in the overweight group than in the normal weight group ($P < 0.01$). The proportion of patients who underwent mammography also gradually increased with an increase in BMI ($P < 0.01$). The proportion of patients who underwent modified radical mastectomy was significantly lower in the overweight and obese groups compared with the normal weight and underweight groups. However, the proportion of patients who underwent SLNB and BCS was significantly higher in the overweight and obese groups than in the normal weight and underweight groups ($P < 0.01$). No significant differences were observed in other clinicopathological characteristics and the implementation rate of preoperative B-ultrasound examinations among the BMI groups (data not shown).

Analysis of the associations between breast cancer subtypes and BMI

In the population of premenopausal women with breast cancer, the TN type was significantly more frequent than the luminal A type in the obese group compared with the underweight group ($P < 0.01$) (Table 7). In the postmenopausal population, the opposite trend was observed, where the TN type was significantly less frequent than the luminal A type in the obese group compared with the underweight group ($P < 0.01$).

Discussion

At present, most research on the association between BMI and breast cancer has been carried out in Western developed countries.[17] However, research on this association in the Asian population, especially East Asian populations, such as the Chinese, is relatively less than that in Western countries.[18] There is a large difference between Western and East Asian populations regarding dietary habits and sociocultural factors.[19] Therefore, the effect of BMI on the occurrence and development of breast cancer is also likely to differ between these countries, and this in turn should be reflected in the national prevention strategies for breast cancer. Additionally, findings in the Chinese population can be applied to other developing countries because certain socioeconomic factors are similar among developing countries.

In our study, we found that the distribution of the BMI subgroups was different compared with that in Western populations. The normal weight group comprised more than 60% of the population, followed by the overweight (26.6%), and finally, the underweight and obese groups (approximately 5% in each group). The proportion of BMI in the normal weight group was significantly higher and that in the obese group was significantly lower than those in Western populations.[20] Furthermore, the distribution of BMI is similar to that reported by other Chinese and Japanese scholars.[4,16] This difference between Western and Eastern populations may be attributable to factors related to social background, living habits, and income.[19] These differences should be reflected in the manner of detection, the treatment method, and therefore, the clinicopathological features and distribution of the molecular phenotype. This was indicated by the findings in the present study.

In our study, the tumor diameter significantly increased, the proportion of patients with the early stage of breast cancer gradually decreased, and the proportion of patients with the advanced stage of breast cancer gradually increased with an increase in BMI. These results are similar to those of a recent study conducted by other Chinese scholars.[16] A possible reason for these findings is that a lower BMI represents less breast volume, and therefore, earlier discovery of breast masses. This could explain the higher proportion of patients with early-stage breast cancer with a low BMI.

In a previous study, we found that demographic factors affected the manner of diagnosis and treatment.[21] Therefore, in the present study, we also examined the effect of BMI on the diagnosis and treatment of breast cancer because BMI is also closely related to patients' demographic factors. Detection at the time of a regular physical examination means that the chances of diagnosing breast cancer at its early stages are higher. Therefore, these patients receive timely medical care. With a gradual increase in the tumor mass, and therefore, disease stage, the chances of accidental discovery by patients while taking a shower or changing clothes are higher. Therefore, the chances of delayed diagnosis are higher. With further progression of disease, symptoms (e.g., mass ulceration, skin involvement, nipple retraction, and pain) will gradually appear, and there is a further delay in diagnosis. In this study, we found that with an increase in BMI, the proportion of patients in whom breast cancer was found by a physical examination or by chance significantly gradually increased, and that of patients in whom this disease was detected on the basis of symptoms gradually decreased. In the Chinese population, the income of most individuals who are obese or overweight is higher than that of individuals who are underweight, who are mostly manual workers and rural dwellers.[19] Because rural medical and health conditions are poor compared with city conditions, this difference in income and medical and health resources could explain the difference in the manner of diagnosis.[22] However, lean women are likely to have less breast volume and thus are more likely to detect masses on their own. This could explain why the incidence of tumor detection through a physical examination was low in the underweight group.

The two most common preoperative examinations reflected a similar trend across the BMI groups in our study With an increase in BMI, the implementation rate of mammography gradually increased, and B-ultrasound examinations also showed a similar trend. This trend may be related to the economic conditions of the patients. Because the cost of mammography is high, lower income populations cannot afford it. Furthermore, people with a lower income usually live in low-income communities, and community hospitals in such areas usually cannot afford such advanced and expensive equipment. Shaanxi is a low-income area. Therefore, delayed diagnosis and infrequent breast cancer screening are common. We hope that these findings emphasize the need for more frequent breast cancer screening programs and thus timely diagnosis and better implementation of preoperative examinations.

Socioeconomic conditions of the patients and their locality affect the surgical approach. In this study, we found a significant difference in the type of treatment used across different BMI populations. With an increase in BMI, the implementation rate of radical surgery (modified radical mastectomy) gradually decreased, and the implementation rate of advanced surgical techniques (SLNB or BCS) increased. The higher rates of SLNB and BCS in the higher BMI groups could be explained by the higher income and ability to accept new ideas and new technology in these groups.[23] Furthermore, the lower income population (mostly comprised the underweight group) might not have been able to afford the cost of radiotherapy after BCS. Additionally, this part of the population usually lives in poorer areas, where radiotherapy is not easily available. Another important point is that patients with a relatively large breast volume (from the overweight and obese groups) are more likely to undergo BCS. At present, SLNB and BCS are the main operative modes for treating breast cancer in developed countries.[24] The results of this study suggest that developed countries should provide medical assistance to less developed areas, so that patients in these regions can benefit from technological advances in this field.

The female menopausal age is usually approximately 51 years in China and the retirement age for women is 50 years.[25] Therefore, differences in the economic ability of women are likely to exist before and after retirement, which would be reflected in the diagnosis and treatment of breast cancer. Our study showed that, in premenopausal patients, there was a considerable difference in the choice of surgical operation between the BMI groups. A higher number of patients in the overweight and obese groups than in the underweight and normal weight groups selected SLNB and BCS, while an opposite trend was observed for radical surgery. These results were similar to those of the total patient population. In postmenopausal patients, the BMI groups showed significant differences in the tumor size, stage, manner of detection, implementation rate of preoperative examinations, and surgical approach. The overall trend in differences was in accordance with the trend in the total population. Finally, the results of the stratified analysis showed that the Chinese retirement system does not appear to be associated with implementation of diagnosing breast cancer and treatment strategies in women.

We also investigated another important factor, which was the relationship between BMI and the molecular phenotype of cancer. This is currently a hot research topic in related fields. At present, most scholars believe that increased BMI is a risk factor for breast cancer only in postmenopausal women, and that it mainly increases the risk of hormone receptor-positive breast cancer;[26] However, other scholars believe that this increased risk is not necessarily limited to certain molecular subtypes.[16] Additionally, some researchers have found that increased BMI in premenopausal women with breast cancer is mainly found in those with TN type cancer,[7] but this correlation is not observed in postmenopausal patients. In contrast, some scholars have found an association between BMI and the TN type in postmenopausal patients,[4] and some scholars have even found that the TN type is negatively correlated with an increase in BMI.[27] In our study, we observed a relationship between BMI and the molecular type of the breast cancer in the overall patient population, as well as in the premenopausal and postmenopausal patient populations. In the overall patient population, the BMI subgroups and molecular subtype were not obviously correlated, but in the premenopausal and postmenopausal populations, remarkable differences were observed in the distribution of molecular phenotypes between the BMI groups. Case-only OR analysis showed that, in the premenopausal population, the TN type was more likely to be found in the obese group, while in the postmenopausal population, the luminal A type was more likely to appear in the obese group. This finding is consistent with most reported studies.[4,7] This association is probably attributable to the positive relationship between BMI and endogenous estrogen levels because adipose tissue is the primary source of estrogen in postmenopausal women. Increased endogenous estrogen levels can increase the risk of luminal type breast cancer. Obesity among premenopausal women is associated with lower estrogen levels, possibly due to irregular menstruation and anovulation. This may explain why an elevated BMI increased the risk of TN type tumors. The reason for the diverse research results is probably attributable to differences in race, social background, and research method, among other factors, used across different studies.

There are some potential limitations to our study. First, a total of 256 (256/1296, 19.8%) patients were excluded because the tumor cells had a 2+ Her2 score and were not assessed by FISH, and some clinicopathological data were missing. Second, we did not set a healthy population as the control. Third, most of our patients were from Shaanxi Province, which is in the center of China, and this may not have been completely representative of the entire Chinese ethnic population. Finally, the classification of tumor subtypes as defined in our study is not identical to other published data because of a lack of information on other tumor markers, such as cytokeratin 5/6 and epidermal growth factor receptor.

Conclusions

Our study shows that a higher BMI is associated with a larger tumor size, more advanced disease stage, diagnosis by a physical examination, higher implementation rate of preoperative examinations, and lower radical surgery rate in Chinese women with breast cancer. These effects differ between the premenopausal and postmenopausal populations. Furthermore, the relationship between BMI and the molecular phenotype of the cancer is not entirely consistent across the population, especially between pre- and postmenopausal women. In premenopausal patients, the TN type is more likely to be found in obese women, and in postmenopausal women, the luminal A type is more likely to appear in obese women. The findings from this study can be applied to other developing countries. In particular, our findings shed light on the need for more screening programs to ensure timely detection of breast cancer and the introduction of advanced techniques to ensure proper treatment in developing regions.

Acknowledgement

We would like to thank the native English-speaking scientists of Elixigen Company for editing our manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the National Natural Science Fund of China (number: 81702633).

Authors' contributions

BW, LZZ, SYJ, LZZ, YHZ, LGN, YY, and KW managed the study, conducted the literature review, and prepared the manuscript. KW, BW, LZZ, and SYJ designed the study and performed statistical analysis. BW, LZZ, SYJ, LZZ, YHZ, LGN, and YY contributed to the study material, interpretation of data, and critical revision of the manuscript.

References

1. Anderson BO and Jakesz R. Breast cancer issues in developing countries: an overview of the Breast Health Global Initiative. *World J Surg* 2008; 32: 2578–2585. DOI:10.1007/s00268-007-9454-z.
2. Green M and Raina V. Epidemiology, screening and diagnosis of breast cancer in the Asia-Pacific region: Current perspectives and important considerations. *Asia-Pac J Clin Onco* 2008; 4: S5–S13. DOI: 10.1111/j.1743-7563.2008.00191.x.
3. Yang L, Parkin DM, Ferlay J, et al. Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 243–250. DOI: 10.1007/BF02881717.
4. Sueta A, Ito H, Islam T, et al. Differential impact of body mass index and its change on the risk of breast cancer by molecular subtype: A case-control study in Japanese women. *Springerplus* 2012; 1: 39. DOI: 10.1186/2193-1801-1-39.
5. Kawai M, Minami Y, Kuriyama S, et al. Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study. *Br J Cancer* 2010; 103: 1443–1447. DOI: 10.1038/sj.bjc.6605885.
6. Mathew A, Gajalakshmi V, Rajan B, et al. Anthropometric factors and breast cancer risk among urban and rural women in South India: a multicentric case-control study. *Br J Cancer* 2008; 99: 207–213. DOI: 10.1038/sj.bjc.6604423.
7. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008; 109: 123–139. DOI: 10.1007/s10549-007-9632-6.
8. Iwasaki M, Otani T, Inoue M, et al. Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. *Ann Epidemiol* 2007; 17: 304–312. DOI: 10.1016/j.annepidem.2006.09.003.
9. Leong SPL, Shen ZZ, Liu TJ, et al. Is breast cancer the same disease in Asian and Western countries? *World J Surg* 2010; 34: 2308–2324. DOI: 10.1007/s00268-010-0683-1.
10. Li J, Zhang BN, Fan JH, et al. A Nationwide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in China. *BMC Cancer* 2011; 11: 364. DOI: 10.1186/1471-2407-11-364.

11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157–163. DOI: 10.1016/S0140-6736(03)15268-3.
12. Types histologiques des tumeurs du sein deuxième édition Organisation Mondiale de la Santé Genève, 1981 [Histological typing of breast tumors. Second edition. World Health Organization. Geneva, 1981]. *Ann Pathol* 1982; 2: 91–105.
13. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC Cancer Staging Manual: Breast Cancer. *Ann Surg Oncol* 2018; 25: 1783–1785. DOI: 10.1245/s10434-018-6486-6.
14. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* 2007; 131: 18–43. DOI:10.1200/JCO.2006.09.2775.
15. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; 22: 1736–1747. DOI: 10.1093/annonc/mdr304.
16. Chen FY, Ou HY, Wang SM, et al. Associations between body mass index and molecular subtypes as well as other clinical characteristics of breast cancer in Chinese women. *Ther Clin Risk Manag* 2013; 9: 131–137. DOI: 10.2147/TCRM.S41203.
17. Kabat GC, Kim MY, Lee JS, et al. Metabolic obesity phenotypes and risk of breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2017; 26: 1730–1735. DOI: 10.1158/1055-9965.EPI-17-0495.
18. Iyengar NM, Chen IC, Zhou XK, et al. Adiposity, inflammation, and breast cancer pathogenesis in Asian women. *Cancer Prev Res (Phila)* 2018; 11: 227–236. DOI: 10.1158/1940-6207.CAPR-17-0283.
19. Yang GH, Ma JM, Liu N, et al. Study on diet, physical activities and body mass index in Chinese population in 2002. *Chin J Epidemiol* 2005; 26: 246–251.
20. Demirkan B, Alacacioglu A and Yilmaz U. Relation of body mass index (BMI) to disease free (DFS) and distant disease free survivals (DDFS) among Turkish women with operable breast carcinoma. *Jpn J Clin Oncol* 2007; 37: 256–265. DOI: 10.1093/jjco/hym023.
21. Wang K, Li X, Zhou C, et al. Socioeconomic factors influencing tumor presentation and treatment options in Chinese breast cancer patients. *Asian Pac J Cancer Prev* 2013; 14: 267–274. DOI: 10.7314/apjcp.2013.14.1.267.
22. Richardson JL, Langholz B, Bernstein L, et al. Stage and delay in breast cancer diagnosis by race, socioeconomic status, age and year. *Br J Cancer* 1992; 65: 922–926.
23. Keating NL, Weeks JC, Borbas C, et al. Treatment of early stage breast cancer: do surgeons and patients agree regarding whether treatment alternatives were discussed? *Breast Cancer Res Treat* 2003; 79: 225–231. DOI: 10.1023/a:1023903701674.
24. Povoski SP, Jimenez RE, Wang WP, et al. Standardized and reproducible methodology for the comprehensive and systematic assessment of surgical resection margins during breast-conserving surgery for invasive breast cancer. *BMC Cancer* 2009; 9: 254. DOI: 10.1186/1471-2407-9-254.
25. Chow LW, Lui KL, Chan JC, et al. Association between body mass index and risk of formation of breast cancer in Chinese women. *Asian J Surg* 2005; 28: 179–184. DOI: 10.1016/S1015-9584(09)60338-9.
26. Suzuki R, Rudqvist TR, Ye W, et al. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. *Int J Cancer* 2006; 119: 1683–1689. DOI: 10.1002/ijc.22034.
27. Stead LA, Lash TL, Sobieraj JE, et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res* 2009; 11: R18. DOI: 10.1186/bcr2242.