RESEARCH ARTICLE

A Clinical Database of Breast Cancer Patients Reveals Distinctive Clinico-pathological Characteristics: a Study From Central China

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Abstract

Background: Breast cancer is the most common malignant tumor in females worldwide. Many differences exist in clinico-pathological characteristics of breast cancer patients between China and Western countries. This study aimed to analyze clinico-pathological characteristics of breast cancer from central China. Methods: Clinico-pathological information on breast cancer from three hospitals in central China was collected and analyzed. Results: From 1994 to 2012, 2,525 patients with a median age 50 years were included in this study. The 45-49-year age group and invasive ductal carcinoma not otherwise specified accounted for the highest proportions (19.1%, 480/2,525 and 81.0%, 1,982/2,446). Stages 0-I, II and III accounted for 28.0% (682/2,441), 48.4% (1,180/2,441), and 23.7% (578/2,441), respectively. Distribution of N stage showed that N0 accounted for 53.2% (1,344/2,525), and proportion of N0 rose from 51.1% (157/307) in 30-39-year age group to 64.3% (110/171) in ≥ 70-year age group, with an average increase of 2.1% in each age group. Modified radical mastectomy, radical mastectomy, breast-conserving surgery and simple mastectomy were performed for 71.8% (1,812/2,525), 18.0% (454/2,525), 5.2% (131/2,525) and 2.6% (66/2,525), respectively. Proportions of breast-conserving surgery in age ≤ 44-year group (68/132, 51.5%) and simple mastectomy in age ≥ 60-year group (57/89, 64.0%) were higher than in the other age groups. Breast cancers positive for estrogen receptor accounted for 53.0% (1,107/ 2,112). The comparisons among this study and other reports showed higher proportion of younger patients, lower proportion of breast-conserving surgery and positive estrogen receptor patients in China than western countries. Conclusions: Clinico-pathological characteristics in this study demonstrated clear differences between the center of China than Western countries. Additional classification systems should be developed to guide grading of early breast cancer more accurately, especially for N0 patients. Invasive ductal carcinoma is a focus for intensive research.

Keywords: Breast cancer - clinico-pathological characteristics - China

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Introduction

Breast cancer (BC) is the most frequent malignant tumor and the leading cause of cancer death in females worldwide (Jemal et al., 2011). Compared with North American and European countries, although incidence of BC in African, Latin American and Asian countries remains at a low level, it is on steady and rapid increase in these areas (Al-Hashimi et al., 2014; Forouzanfar et al., 2011; Jemal et al., 2011). Epidemiological studies also reveal that BC in Asian countries including China, is undergoing a transition to the pattern of Western countries (Fan et al., 2009; Shin et al., 2010; Ko et al., 2012; Afsharfard et al., 2013).

Although BC in Chinese population shares several similarities with that of Western countries, many different features remain to be explored. Analysis on clinico-pathological characteristics of BC could provide more information on the tendency of BC, so as to help design more pertinent population-based preventive and therapeutic strategies. There have been several studies on the demographic, clinical and pathological characteristics of BC in China, which showed many differences in BC features between Chinese patients and those from Western countries, such as younger onset age, higher proportion of negative hormone receptors, and lower incidence. While those studies have been mainly conducted in socio-economically developed areas of China such as Shanghai (Fan et al., 2009), Hong Kong (Kwong et al., 2011) and Beijing (Pan et al., 2013), there have been no large-scale

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clinical studies from central China, a vast region of China's hinterland with lower socio-economic developments. Therefore, this work was aimed to study characteristics of BC in Chinese population in central China by analyzing clinico-pathological information of BC from three tertiary referral hospitals from Wuhan Municipality, the largest population hub in the central China.

Materials and Methods

Patients

Detailed clinico-pathological information on BC patients from three tertiary-referral hospitals (Zhongnan Hospital of Wuhan University, Renmin Hospital of Wuhan University, and Central Hospital of Wuhan Municipality) were consecutively collected from Jan 1994 to Dec 2012, with complete information available on 2,831 patients for this analysis. The inclusion criteria were the BC patients who received surgical treatments in these three hospitals. The exclusion criteria were male BC, bilateral BC, breast sarcomas, recurrent or metastatic BC, patients with simple excision of the breast tumor without further treatment, and those receiving radio/chemotherapy without surgery. Based on these criteria, 2,525 eligible patients were included in this study. This study protocol was approved by the Institutional Ethics Committee of Zhongnan Hospital of Wuhan University and undertaken according to the ethical standards of the World Medical Association Declaration of Helsinki.

Study parameters and their definition

Major clinico-pathological parameters were systematically investigated in this study. In terms of age and menstrual status, all patients were divided into three age groups: young age group (≤ 44 years), middle age group (45-59 years) and old age group (≥ 60 years). There were 1,232 (51.2%) pre-menopausal cases and 1,293 (48.8%) post-menopausal cases. In terms of surgery-based multidisciplinary therapies, all patients received one of the following surgical treatments: radical mastectomy (RM), modified radical mastectomy (MRM), simple mastectomy (SM), breast-conserving surgery (BCS), and other surgical procedures included extensive radical mastectomy, reconstruction, or endoscopic surgery, all of which were performed according to the current guidelines.

The surgically removed specimens were histo-pathologically classified according to the 4th edition of World Health Organization (WHO) classification system (Lakhani et al., 2012). Immunohistochemical assays were conducted to detect for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) expressions by standard technical procedures and results evaluation criteria in the pathological departments of the three hospitals. Positive HER2 indicated over expression and was identified by a score of 3+, negative HER2 defined as a score of 0, 1+ and 2+ (Zarbo and Hammond, 2003). The final pathological tumor-node-metastasis (TNM) stages of all patients were re-staged according to the 7th edition of American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM system (Edge et al., 2010).

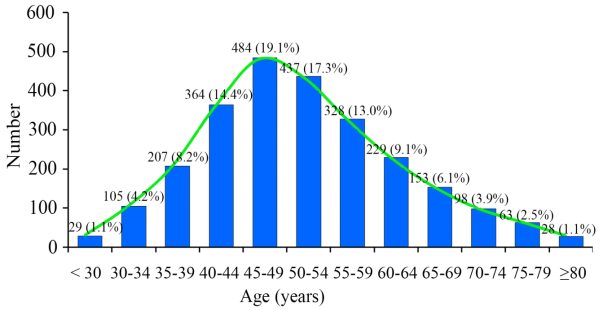

Figure 1. Age Distribution of BC Patients in this Study. Age group frequencies and proportions by 5-year intervals were listed. The age distribution curve is not symmetric, with the highest proportion in the 45-49-yr group (19.1%, 480/2,525)

Statistics

Statistical methods consisted of frequency and chi-square (χ^2) analyses for categorical variables (Fisher's exact test was adopted if χ^2 test was not applicable). Student's t test was performed to compare differences in means. Binomial test was used to compare the differences between each age group and the overall population. Statistical analysis was performed by SPSS 17.0 (SPSS Inc. Chicago, IL, USA). Two-sided $P < 0.05$ was judged as statistically significant.

Results

Age distribution of BC patients

There were 2,525 eligible cases in our database, including 1,546 (61.2%) patients from Zhongnan Hospital of Wuhan University, 363 (14.4%) patients from Renmin Hospital of Wuhan University and 616 (24.4%) patients from Central Hospital of Wuhan Municipality, respectively. Age distribution of these patients ranged from 22 to 87 years (median age 50 years), and age group frequencies by 5-year intervals were listed in Figure 1. There were 705 (27.9%), 1,249 (49.5%) and 571 (22.6%) cases in young, middle and old age groups, respectively. In terms of menstrual status, 1,189 (47.1%) cases were pre-menopausal and 1,336 (52.9%) cases post-menopausal. The 45-49-yr group accounted for the highest proportion (19.1%, 480/2,525), followed by the 50-54-yr group (17.3%, 434/2,525) and the 40-44-yr group (14.4%, 364/2,525).

From Figure 1, several facts deserve special attention. First, the age distribution curve is not symmetric, with steeper increases before 45-49-yr group and slower decreases thereafter. Second, there is a sharp increase in BC incidence rate by over 6% before age 40 years. This increase exceeds all other subgroups. Third, 47.0% of BC patients are in < 50-yr age group, and 13.5% of BC patients are in the < 40-yr group.

Distribution of surgical treatment procedures

In this study, all patients received surgical treatments, with MRM accounting for 71.8% (1,812/2,525), RM for 18.0% (454/2,525), BCS for 5.2% (131/2,525), and SM for 2.6% (89/2,525) (Figure 2A). Taking 2002 as a dividing time point, it was observed that operation with less physical disfigurement and psychological trauma became

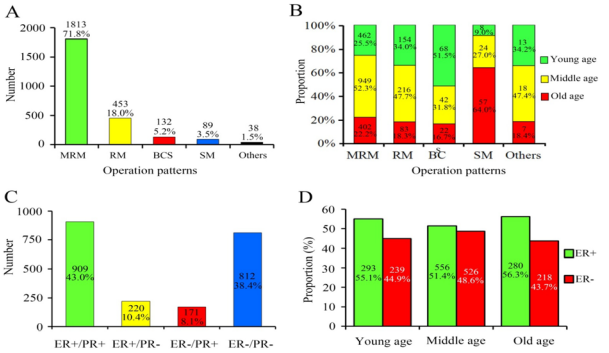

Figure 2. Distribution of Operation Patterns, ER and PR Status for BC Patients in This Study. Number of different operation patterns (A) and ER+/PR+, ER+/PR-, ER-/PR+ and ER-/PR- (C); proportion of operation patterns (B) and hormone receptor status (D) in different age groups (D). MRM: modified radical mastectomy; RM: radical mastectomy; BCS: breast-conserving surgery; SM: simple mastectomy; Others: extensive radical mastectomy, reconstruction, or endoscopic surgery. ER: estrogen receptor; PR: progesterone receptor

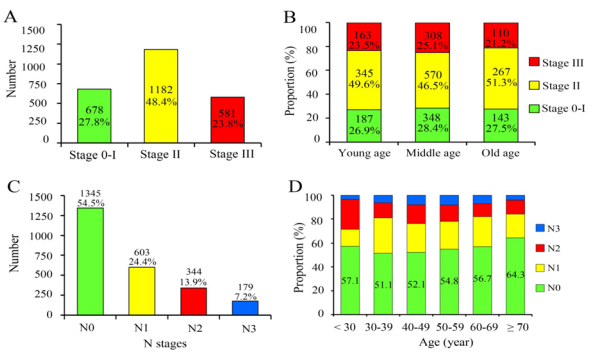

Figure 3. TNM and N Stages for Breast Cancer Patients in This Study. Distribution of TNM (A) and N stage (B); distributions of TNM stage (B) and proportion for N stages (D) in different age groups (B). TNM: tumor-node-metastasis

more popular. Proportion of RM was 4.9% (91/1,852) after 2002, which was significantly lower than 53.8% (53.8%, 362/673) before 2002 ($\chi^2 = 800.96$, $P < 0.001$). While, proportions of MRM and BCS after 2002 were 85.4% (1,582/1,852) and 4.9% (7.1%, 123/1,852), which were significantly higher than corresponding proportions (MRM 34.3%, 231/673; BCS: 1.3%, 9/673) before 2002 ($\chi^2 = 636.55$, $P < 0.001$ for MRM after 2002 vs before 2002; $\chi^2 = 25.87$, $P < 0.001$ for BCS after 2002 vs before 2002).

Figure 2B showed proportions of different age groups in each operation patterns. Proportion of old age was higher in SM group (64.0%, 57/89) than in MRM group (22.2%, 402/1,813), the second high group of these five groups ($\chi^2 = 81.238$, $P < 0.001$). Proportion of young age was higher in BCS (51.1%, 68/132) than others group (34.2%, 13/25) ($\chi^2 = 13.323$, $P < 0.001$). The differences among proportions of middle age group in MRM (52.3%, 949/1,813), RM (47.4%, 216/453) and others groups (47.4%, 18/38) had no statistical significance ($\chi^2 = 3.398$, $P = 0.183$). Proportion of middle age was higher in RM group than in BCS group ($\chi^2 = 10.435$, $P = 0.001$).

Proportions of operations patterns in different age groups and overall were also analyzed. Proportions of MRM in young age group (65.5%, 462/705; $P < 0.001$), RM in old age group (14.5%, 83/571), BCS in middle age group (3.4%, 42/1,249), SM in young age group (1.1%, 8/705)) and middle age group (1.9%, 24/1,249) were significantly lower than corresponding operations in overall (MRM young age vs overall: $P < 0.001$; RM old age vs overall: $P = 0.016$; BCS middle age vs overall: $P = 0.003$; SM young age vs overall: $P < 0.001$, middle age vs overall: $P = 0.001$). Proportions of MRM in middle age group (76.0%, 949/1249), RM in young age group (21.8%, 154/705), BCS in young group (9.6%, 68/705) and SM in old age group were significantly higher than corresponding operations in overall (MRM middle age vs overall: $P < 0.001$; RM young age vs overall: $P = 0.005$; BCS young age vs overall: $P < 0.001$; SM old vs overall: $P < 0.001$).

Hormone receptors status

In all patients, 2,112 cases (83.6%) had clear hormone receptors status information. Those patients were divided into the following four subgroups: ER+/PR+, ER+/PR-, ER-/PR-, and ER-/PR+. ER+/PR+ group accounted for the highest proportion (43.5%, 909/2,112), followed by ER-/PR- (38.9%, 812/2,112), ER+/PR- (9.5%, 198/2,112), and ER-/PR+ (8.2%, 171/2,112) (Figure 2C). Analysis on proportions of ER status in different age-groups showed that proportions of ER+ in all age-groups were higher than ER-. The differences among proportions of ER+ in old age group (56.3%, 280/498), young age group (55.1%, 293/532) and middle age group (51.4%, 556/1,082) had no statistical significance ($\chi^2 = 3.958$, $P = 0.138$) (Figure 2D). There was also no significant statistical differences in proportion of ER+ in overall (53.4%, 1,129/2,112) and the three age groups (overall vs young age: $P = 0.247$; overall vs middle age: $P = 0.086$; overall vs old age: $P = 0.120$).

HER2 expression

Positive HER2 indicated over expression and was identified by a score of 3+, negative HER2 indicated a score of 0, 1+ and 2+. (Zarbo and Hammond, 2003) Immunohistochemical assays on HER2 were popular after 2003, and 59.8% (1,510/2,525) patients had such analysis, 84.0% (1,268/1,510) was defined as negative, and 16.0% (242/1,510) was defined as HER2 positive.

Histological type of BC

According to the most recent WHO classification (2012) for BC, 2,446 patients had definitely pathologic classification. Invasive ductal carcinoma was the most common type of BC accounting for 90.1% (2,205/2,446), followed by invasive lobular carcinoma (3.9%, 95/2,446) and carcinoma in situ (2.2%, 54/2,446) (Table 1). To further study histological type of BC, invasive ductal carcinoma was subdivided into several subtypes according to WHO classification. Invasive ductal carcinoma not otherwise specified accounted for the highest proportion (81.0%, 1,982/2,446) of invasive ductal carcinoma, followed by invasive with predominant intraductal component (4.0%, 97/2,446), mucinous (2.3%, 57/2,446), and medullary (1.4%, 35/2,446).

Table 1. Histo-pathological Types of 2,446 Breast Cancer Patients According to 4th World Health Organization Classification

Histological type	Number (%)
Invasive ductal carcinoma	2,205 (90.1)
Invasive not otherwise specified	1,982 (81.0)
Invasive with predominant intraductal component	97 (4.0)
Mucinous	57 (2.3)
Medullary	35 (1.4)
Miscellaneous*	34 (1.4)
Invasive lobular carcinoma	95 (3.9)
Carcinoma in situ	54 (2.2)
Paget's disease	14 (0.6)
Others	78 (3.2)

*including tubular, papillary, comedo, metaplastic and apocrine types

TNM stage of BC

All patients were re-staged according to the 7th edition AJCC/UICC TNM system. There were 2,441 (96.7%) patients with complete TNM information. Patients with stage IV were excluded from this study, so only proportion of stage 0-I, II and III were shown in Figure 3 (A and B). Patients with stage II accounted for the highest proportion of BC (48.4%, 1,180/2,441), followed by stage 0-I (28.0%, 682/2,441) and stage III (23.7%, 578/2,441) (Figure 3A). Distributions of TNM stage in different age groups (Figure 3B) showed differences in stage 0-I in young age (26.9%, 187/695), middle age (28.4%, 348/1,226) and old age 27.5% (143/520) were small. Proportion of stage II in old age (51.3%, 267/520) was high than young age (49.6%, 345/695) and middle age group (46.5%, 570/1,226) (old age vs young age: $P = 0.556$; old age vs middle age: $P = 0.063$). Proportion of stage III in middle age group (25.1%, 308/1,226) was higher than it in young age group (23.5%, 163/695) and old age group (21.2%, 110/520) (middle age vs young age: $P = 0.414$; middle age vs old age: $P = 0.076$).

N information is very important to TNM stage system. As some patients had limited surgery such as simple mastectomy, which did not remove lymph nodes, 54 cases (2.1%, 54/2,525) patients had no N information. Distribution of N stage for BC showed that N0 accounted for 53.2% (1,344/2,525), followed by N1 (23.9%, 604/2,525), N2 (13.6%, 344/2,525), N3 (7.1%, 179/2,525,) and Nx (2.2%, 54/2,525) (Figure 3C).

In all the other age groups except for the < 30-year group, the proportion of N0 patients increased with age (Figure 3D). The N0 percentage rose from 51.1% in 30-39-year age group to 64.3 % in ≥ 70-year age group, by an average increase of 3.3% in each age group ($\chi^2 = 10.768$, $P = 0.029$). Although the N0 percentage for < 30-year group was 57.1% (16/28), higher than other groups such as 30-39-year group (157/307, 51.1%), 40-49-year group (438/841, 52.1%), 50-59-year group (416/759, 54.8%) and 60-69-year group (212/374, 56.7%), the number of patients in this group was small. Notably, the N0 percentage in the older patients was much higher, 64.3% (110/171) for the ≥ 70-year group.

To further compare the clinico-pathological characteristics in this study with others, we reviewed several large scale studies reported in recent years (Figure 4). Proportions of < 50 years, N0, operation patterns and ER+ have been analyzed in Figure 6. Proportion < 50 years in Asian countries (47.0%-57.3%) was higher than Europeans and American countries (14.8%-30.5%) (Figure 4A). Proportion of N0 in China (46.8%-53.7%) was lower than developed areas (58.0%-71.2%) (Figure 4B). BCS (5.2%-5.6%) and ER+ (53.0%-57.0%) in China mainland is lower than developed areas (BCS: 43.5%-60.6%; ER+: 66.2%-77.1%) (Figure 4C and 4D).

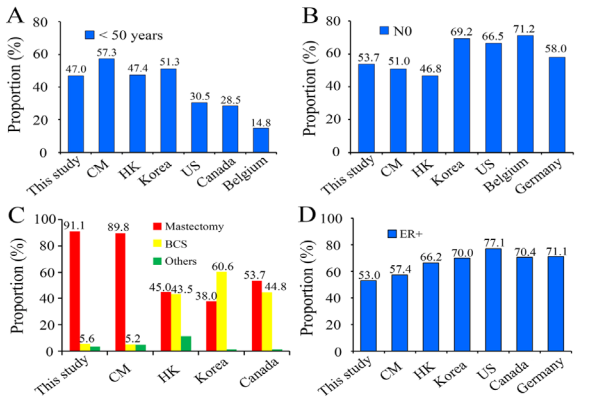

Figure 4. The Comparison among Proportions of Age, N0, Surgical Pattern and ER+ in Different Countries and Regions. Distribution of proportion < 50 years (A), N0 stage (B), operation patterns (C) and ER+ proportions (D) in different regions. CM: China mainland; HK: Hong Kong; US: United States; BCS: breast-conserving surgery; ER: estrogen receptor

Discussion

BC has long been a big burden to global healthcare. The characteristics of BC in Asian, including China are different from Western countries. One notable fact is the relatively younger age of BC for Chinese females. The median age was 50 years in this study, which was similar to Shanghai (50 years) (Fan et al., 2009), Korean (49 years) (Ko et al., 2012), lower than Western developed countries (the United States: 62 years (Anderson et al., 2006); Canada: 60 years (Turashvili et al., 2011); German: 59 years (Fritz et al., 2010); Belgium: 58 years (Brouckaert et al., 2013)). Percentage of BC < 50 years in America was 27.0% (Desantis et al., 2013), much lower than this study (47.0%). Another particularly noticeable finding is that 13.5% of BC patients are in the <40-yr group. Peak incidence of BC occurred among 45-49-yr group, with a steeper increases before peak incidence age group and shower decreases after this age group in this study, which is 10 years younger than that of Western countries (Leong et al., 2010). In addition, a sharp increase in BC incidence rate by over 6% before and after age 40 years. These findings may have important implications in terms of primary prevention of BC in Chinese females (in central China). While more attentions should be paid to the females ≥ 40-year to enhance their awareness, the <40-year age group should also receive special attention. In the same time, more specific instruments with easy access and user friendly processes should be developed to

target such population, such as intensified efforts to spread knowledge and practical skills in BC self-examination and early detection through mass media, particularly the ever-increasing internet services. In some developed areas of China (Hong Kong (Kwong et al., 2011) and Shanghai (Fan et al., 2009)), there were double peak incidences of BC which occurred among 45-50 years and > 65 years, which was different with this study.

Surgery is the principal treatment for BC (Newman, 2004). RM, MRM, BCS, and SM were the 4 common types of BC surgery in China, (Yu et al., 2007; Zhang et al., 2013) accounting for 18.0% (454/2,525), 71.8% (1,812/2,525), 5.2% (131/2,525) and 2.6% (66/2,525) of the cases, respectively, in our study. Because BCS could maintain the shape and function of breast, it has been popular for several decades and become the most common surgical procedure in developed areas such as Korea (60.6%), (Ko et al., 2012) Hong Kong (43.5%) (Kwong et al., 2011) and Canada (44.8%) (Turashvili et al., 2011). However, this treatment is not well-received in China. A multi-center study from China showed that percentage of BCS only was 5.6% from 1999 to 2008, due to social, cultural and economic factors (Zhang et al., 2013). Even in Shanghai, the most developed city of China, BCS only accounted for 13.5% in 2007, much lower than developed countries (Fan et al., 2009). In our study, the percentage of BCS only accounted for 5.2% (131/2,525), which is similar to Zhang's study from China (5.6%) (Zhang et al., 2013). MRM is decreasing and have been a non-mainstream operation pattern in developed countries (Ko et al., 2012; Piscitelli et al., 2012). While, our study showed MRM was still the major surgical treatment accounting for 71.8%, similar to another study from China (79.7%), which is much higher than developed counties/areas (Ko et al., 2012; Turashvili et al., 2011; Wei et al., 2010). As a safe treatment procedure, BCS has been expanded for more than 20 years since the National Institutes of Health Consensus Development Conference Statement was released advising breast conservation (Abrams et al., 1995). However, this surgical approach remains unpopular in China mainland, and greater efforts should be made to spread this treatment strategy (Zhang et al., 2012).

Age may be an influence for the choice on operation patterns in this study. Patients of this study in old age group tend to receive SM (64.0% for old age group, 27.0% for middle group, and 9.0% for young group) and patients in younger age group tend to receive BCS (51.5% for young age group, 31.8% for median age group, and 16.7% for old age group). Similar phenomenon was also reported in other studies (Wei et al., 2010; Yu et al., 2007; Zhang et al., 2013). More psychological and physiological needs exist in young age patients, so BCS is popular in these patients. In contrary, SM is easily received by old age patients. This phenomenon also may be associated with the less malignant behaviors of BC (proportion of N0 patients increased with age in our study) and more co-morbidities in old patients than young patients. So, considering the similar prognosis of people receiving BCS and MRM (Yu et al., 2007) and high percentage of young patients and early stage BC, we conjecture that BCS may be more popular than MRM in China in the future.

Definition on histological type of BC is developing with the knowledge on BC. Recently, WHO published 4th edition of histological classification for BC in 2012 (Lakhani et al., 2012). In this study, invasive not otherwise specified was the most frequent BC, accounting for 81.0% of all BC. This finding was similar to others studies (Ko et al., 2012; Zheng et al., 2012). Because BC is a highly heterogeneous malignant tumor and huge differences exist in biological behaviors of different types of BC (Kumar et al., 2012), studies on BC should be focused on the same histological type. As the most common histological type, invasive ductal carcinoma should be the major object for study.

ER+ BC is more sensitive to endocrine therapy and has a better prognosis than ER-. Percentage of ER+ in our study was 53.0% (983/2,112), which is similar to other studies from China (49.5% to 57.4%) (Kwong et al., 2011; Zheng et al., 2012). Compared with Western countries, proportion of ER+ BC in Asian countries is lower (Leong et al., 2010). In a study by Bigaard et al (Bigaard et al., 2012) in Demark, the incidences of ER+ BC in Danish females were 76.1% (14,906/19,580) and 81.5% (12,719/15,615) for 1996–2002 to 2003–2007, respectively. Bao's study demonstrated that high body mass index, high parity, hormone replacement therapy (HRT) and alcohol consumption appeared to be associated with ER+ type BC (Bao et al., 2011). Long-term exposure to estrogen, such as early menarche, late menopause and HRT), were established risk factors for BC, especially for postmenopausal females (Bao et al., 2011). Prescription of HRT in developing countries including China is lower than developed countries (Bao et al., 2011). The increase of ER+ BC in menopausal females may contribute to increased incidence of BC after menopausal in western countries, incidence was steady for ER- BC (Bigaard et al., 2012; Cronin et al., 2009). This reanalysis using the most recently released data from SEER shows that, the decrease occurred primarily in ER+ BCs, with the rate of ER+ BC in women 50–69 years of age decreasing by 14.5% and ER- BCs are decreasing by 2.1% (Cronin et al., 2009).

Currently, TNM staging system is the universal language to determine the clinical stages of cancer, to predict the prognosis and to guide the treatment options (Fritz et al., 2010). Early stage BC is increasing due to the development of detecting technique on BC and the adoption of mass screening programs. In our study, early stage (stage 0-II) and N0 stage BC accounted for 51.6% and 53.3%, respectively. An interesting finding in this study is the proportion of N0 patients increased with the age which may be associated with the less invasive behaviors of BC in old patients. The dramatic increase in early stage BC has a big impact on the practical utility and academic significance of TNM system in real clinical situation. Although the 5-year overall survival in early BC patients was 91.6% - 92.5% (Kwong et al., 2011; Yu et al., 2007). Therefore, predicting the risk of cancer recurrence and long-term prognosis in early stage BC patients, especially the BC patients without lymph nodes metastasis is an important clinical problem. So, rich information on tumor recurrence and metastasis hidden

in the primary tumor should be explored in future study to supply prognostic information which could not be revealed by the current TNM staging system. Our previous study indicated predictive performance of breast cancer information in situ on prognosis was higher than N stage (Wang et al., 2013). Therefore, with the changing clinical scenario, new staging systems other than TNM staging should be developed to better subdivide early stage BC patients for more appropriate personalized therapies. The new staging system should be an integration of information on gross pathology, histological features and molecular characteristics of the primary tumor.

In conclusion, compared with Western countries, clinico-pathological characteristics in this study showed higher proportion of young patients, lower proportion of BCS and positive estrogen receptor patients. Additional classification systems should be developed to guide grading of early BC more accurately, especially for N0 patients. As a most common histological type, invasive ductal carcinoma not otherwise specified should be the focus for intensive research in future studies.

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