RESEARCH COMMUNICATION

Characteristics of Mammary Paget's Disease in China: a National-wide Multicenter Retrospective Study During 1999-2008

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Abstract

The aim of this study was to detail characteristics of mammary Paget's disease (PD) representing the whole population in China. A total of 4211 female breast cancer inpatients at seven tertiary hospitals from seven representative geographical regions of China were collected randomly during 1999 to 2008. Data for demography, risk factors, diagnostic imaging test, physical examination and pathologic characters were surveyed and biomarker status was tested by immunohistochemistry. The differences of demography and risk factors between PD with breast cancer and other lesions were compared using Chi-square test or t-test, with attention to physical examination and pathological characters. The percentage of PD was 1.6% (68/4211) in all breast cancers. The mean age at diagnosis was 48.1, and 63.2% (43/68) patients were premenopausal. There is no difference in demography and risk factors between PD with breast cancer and other breast cancer (P > 0.05). The main pattern of PD in physical exam and pathologic pattern were patients presenting with a palpable mass in breast (65/68, 95.6%) and PD with underlying invasive cancer (82.4%, 56/68) respectively. The rate of multifocal disease was 7.4% (5/68). PD with invasive breast cancer showed larger tumor size, more multifocal disease, lower ER and PR expression and higher HER2 overexpression than those in other invasive breast cancer (P < 0.05). These results suggested that PD in China is a concomitant disease of breast cancer, and that PD with underlying invasive cancer has more multiple foci and more aggressive behavior compared with other breast invasive cancer. We address the urgent needs for establishing diagnostic and therapeutic guidelines for mammary PD in China.

Keywords: Paget's disease - breast disease - characteristics - ethnic populations - China

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Introduction

Paget's disease (PD) of the nipple is a rare condition in breast cancer. It was first described by Sir James Paget in 1874 (Paget, 1874), which found certain chronic affections of the skin of the nipple and areola, and then succeeded by breast cancer. PD of the breast always represented an early appearance of eczema affecting the nipple and the areola, so the diagnosis and treatment were always delayed (Ashikri et al., 1970; Fu et al., 2001).

In the Western countries, PD is more common in older post-menopausal female. There are two patterns of PD in physical examination (Sakorafas et al., 2001): patients present with or without a palpable mass in the breast. There are three pathologic patterns of PD: PD with underlying invasive cancer, PD with underlying ductal carcinoma in situ (DCIS) and PD with absence of an underlying pre-cancerous or cancerous condition of the breast (Nance et al., 1970). The patterns of physical examination may hint the pathologic result. Patients with palpable mass in physical examination are always found invasive cancer and lymph node metastases (LNM) in pathology, while patients without palpable mass in physical examination are always found DCIS or without absence of an underlying pre-cancerous or cancerous condition of breast and no LNM. There are two theories on the hypothesis of the nature and origin of PD: the epidermotropic theory and in-situ malignant transformation theory (Ashikri et al., 1970; Paone and Baker, 1981; Mai et al., 1999). The former theory postulates that Paget's cells are duct cancer cells that have migrated along the basal membrane of underlying ducts

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to the epidermis of the nipple. The latter theory regards the Paget's cells as malignant keratinocytes appearing in situ and PD as an in situ carcinoma, independent of any underlying pre-cancerous or cancerous condition. In recent years, researches had found that human epidermal growth factor receptor 2 (HER2) and vimentin filaments may be related to the pathogenesis of PD (Hanna et al., 2003). Mastectomy was the standard therapy in patients with PD for many years, while breast conservation therapy followed by postoperative breast irradiation is now being selectively considered in unifocal disease. There are also some reports of breast radiation therapy alone in PD treatment with various results (Sakorafas et al., 2001). As the outcome of PD is determined by the underlying associated cancer, chemotherapy and endocrine therapy should be given when necessary. The algorithms for the clinical management of patients with PD of the breast were proposed in recent years (Sakorafas et al., 2001).

China was one of the low- and middle-income countries (LMCs), which reported breast cancer incidence rates increasing quickly (Chen and Kong, 2010; NOCPC, 2010). There were few reports about characters of PD in LMCs besides China (Liu et al., 2000; Wang et al., 2002; Sun et al., 2003; Yu et al., 2005; Di et al., 2007; Meibodi et al., 2008). This may hold back the improvement of the clinical management in PD in these countries. Our previous studies found that there were obvious difference of pathologic characters in breast cancer between the Western and China (Li et al., 2011; Zheng et al., 2012). We wondered whether there were also some differences in PD between the two populations. As a part of series researches, the aim of this study was to perform a detailed study on characteristics of PD representing the whole population in China during 1999 to 2008. We firstly summarized the general information of PD during 1999-2008 from all seven traditional China regions. Then, we compared the differences of demography, risk factors between PD with breast cancer and other breast cancer. At last, we compared the difference of physical examination and pathologic characters of PD with invasive cancer and other invasive cancer. We hoped this may help to improve the clinical management of mammary PD both in China and other LMCs where mammary PD had not been well studied.

Materials and Methods

This study was a constitutive part of a multi-center retrospective hospital-based research focused on Chinese women with primary breast cancer, which had passed the review of the Ethics Committee of Cancer Foundation of China. The methodology was described in detail before (Li et al., 2011). In brief, there were seven tertiary hospitals from all seven traditional China districts selected in this study. The seven districts were north, northeast, northwest, central, east, south and southwest of China, which showed different levels of breast cancer burden (NOCPC, 2010 Li et al., 2011). All the hospital had the abilities of comprehensive therapy of cancer and could represent for the regional patients resource. Every hospital collected patients randomly for no less than 50 cases in any month from March to December by an enrolment scheme during 1999 to 2008. All cases collected with quality control.

All the information was extracted from the primary medical reports, including demography, risk factors, diagnostic imaging test, therapy model, physical exam and pathologic characteristics. Histological subtype was referred to 1981 and 2003 WHO histological classification criterion (Tavassoli and Deviee, 2003; WHO, 1981). Staging of breast cancer was referred to 1997 and after American Joint Committee on Cancer (AJCC) stage criterion (AJCC, 1997; AJCC, 2002). Diagnostic imaging resource allocation was referred to the guideline from Breast Health Global Initiative (BHGI) Consensus Conference (Shyyan et al., 2008). In brief, at basic level, diagnosis is made on clinical history and clinical breast examination without any imaging services, while breast ultra sound is added to diagnose at limited level. With enhanced-level, mammography is usually applied to diagnosis with or without ultra sound. With maximal-level, significant cost imaging services are used for diagnosis with or without ultra sound or mammography, such as breast MRI. The expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 were detected by immunohistochemistry using ER (Clone: SP1, Neomarkers), PR (Clone: SP2, Neomarkers) and HER2 (Clone: A0485, Dako) antibodies. ER, PR, and HER2 status were primarily extracted from medical records. In this study, only patients scored as 3+ were considered HER2 positive (HER2+), which indicating overexpression of HER2. Patients with HER2 scores as 0, 1+, 2+ were considered HER2 negative (HER2-) (Zarbo and Hammond, 2003). Multifocal disease was defined as two or more discontinuous foci of carcinoma involving more than one quadrant in addition to the nipple and immediately underlying breast parenchyma in physical

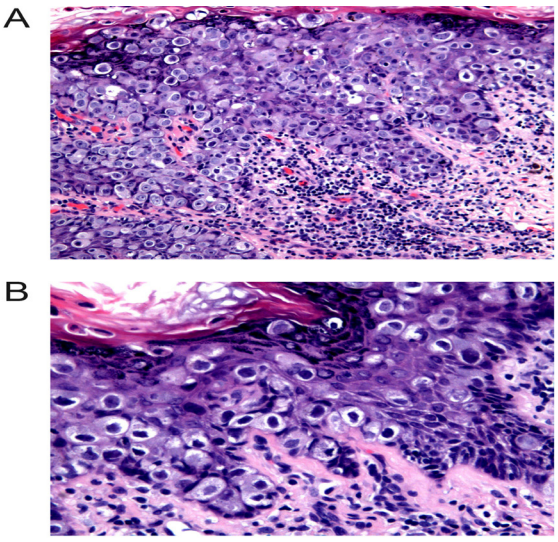

Figure 1. PD of the Nipple Microscopically (A-B) on HE-stained Paraffin-embedded Sections. (A) In the mammary epidermis, there is invasion of atypical cells (Paget's cell). These atypical cells may be single or small clusters and distribute the whole thickness of the squamous epidermis. Inflammatory cells are always detectable in dermis (HE x 100). (B) The Paget's cell shows large hyperchromatic nuclei with abundant clear or focally dense cytoplasm (HE x 200)

examinations.

The relationship between pathologic characters and physical examinations were analyzed. The comparisons of demographic and risk factor exposures were conducted between PD with breast cancer and other breast cancer. Other breast cancer was defined as breast cancer without PD. The characteristics of physical examinations and pathological tests were compared between PD with underlying invasive cancers and other invasive cancer. Other invasive cancer was defined as invasive cancer without PD. Age, body mass index (BMI) and other continuous variables, were analyzed by t tests of two independent samples. Categorical variables were analyzed by Chi-square test. The ordinal variables more than two levels were analyzed by Cochran-Armitage test. Statistical significance was assessed by two-tailed tests with $P< 0.05$. All the statistical analyses were performed using the software SPSS 16.0 (SPSS Inc. Chicago, IL, USA).

Results

A total of 4211 primary breast cancer patients had been included randomly in this study which accounts for 9.3% of the total 45,200 patients with breast cancer during 1999-2008 (Li et al., 2011). There were 68 patients diagnosed with mammary PD, representing 1.6% of the selected patients (68/4211). Table 1 summarized the general information of mammary PD from seven districts during 1999-2008. All the patients took surgical therapy except for two, whose surgery information was not available. The predominant surgical model was mastectomy. Other therapy model included chemotherapy (n=55), postoperative breast irradiation (n=13) and endocrine therapy (n=11). The average age was 48.1 (SD=10.9), which was more common in patients younger than 60 (54/68, 79.4%). Figure 1 showed the representative manifestation of PD microscopically. Paget's cells were distributed in the forms of single or clusters throughout the whole squamous epithelium. They always accompanied the infiltration of inflammatory cells in dermis (Figure 1A). Paget's cells showed obvious atypical of large hyperchromatic nuclei. They had abundantly clear or focally dense cytoplasm (Figure 1B). We divided tumor/lesion size into three groups: ≤ 2 cm, > 2-5 cm and >5 cm. Table 2 listed the information of physical examinations and pathological characters in mammary PD. The predominant physical examinations pattern of PD was patients present with a palpable mass in the breast (65/68, 95.6%). The predominant pathologic patterns of PD was PD with underlying invasive cancer (n=56, 82.4%). The pathologic types of PD with invasive cancer were 52 invasive ductal carcinoma (52/56, 92.9%) and three invasive lobular carcinoma (3/56, 5.3%), while one patient did not assign the pathologic type (1/56, 1.8%). Patients with palpable mass were more likely positive in LNM (27/65, 41.5%) and more likely in PD with underlying invasive cancer (55/65, 84.6%). Multifocal diseases were found in five patients (7.4%, 5/68).

Table 3 listed the differences of demography and risk factors exposure between mammary PD and other breast cancer. We compared age, menstrual status, educational level, parity, breastfeeding, age at menopause, family breast cancer history and BMI, et al. The demography and risk factors exposure were similar in both two groups ($P > 0.05$).

Table 4 and Figure 2 show the comparison of physical examinations between PD with underlying invasive cancer and other invasive cancer. There was statistical

Table 1 The General Information of Mammary PD During 1999-2008 from all Seven Districts in China

Information	Percent
Percentage of mammary PD per year	0.5% (2/403)-4.8% (22/462)
Percentage of mammary PD from different districts	0.7% (6/832)-3.5% (19/546)
Diagnostic imaging resource allocation	
Basic level	26.5% (18/68)
Limited level	33.8% (23/68)
Enhanced level	29.4% (20/68)
Maximal level	2.9% (2/68)
Unknown	7.4% (5/68)
Surgery	
Mastectomy	86.8% (59/68)
Breast-conserving therapy	10.2% (7/68)
Unknown	3.0% (2/68)

PD, Paget's disease

Table 2. The Information of Physical Examination and Pathological Characters of PD of the Nipple in China (n=68)

Pathological characters	Physical examination	
	Palpable mass n (%)	Non-palpable mass n (%)
Histological type, n (%)		
PD with invasive cancer	55 (84.6)	1 (33.4)
PD with DCIS	5 (7.7)	1 (33.3)
PD with absence of an underlying pre-cancerous or cancerous condition	5 (7.7)	1 (33.3)
Total	65 (100.0)	3 (100.0)
LNM, n (%)		
+	27 (41.5)	0 (0.0)
-	33 (50.8)	3 (100.0)
Unknown	5(7.7)	0
Total	65 (100.0)	3 (100.0)

DCIS, ductal carcinoma in situ; LNM , lymph node metastasis; PD, Paget's disease; +, Positive; - , Negative

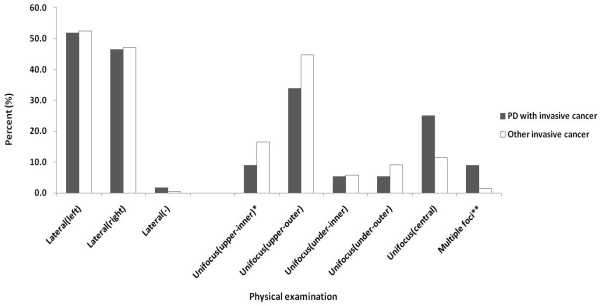

Figure 2. The Relationship Between Physical Examination and Pathology Result of Mammary PD. Gray bars represent physical examination result of mammary PD with invasive cancer. White bars represent physical examination result of other invasive cancer. *significant difference < 0.001; **significant difference < 0.05. Unknown cases are not shown in the figure

Table 3 Comparison in Demography and Risk Factors Between Mammary PD and Other Breast Cancer*

Demography or risk factors	Mammary PD (n=68)	Other breast cancer (n=3840)	P value
Demography			
Age (Mean±SD, n)	48.1±10.9, 68	48.7±10.4, 3840	0.66
Menopause, n (%)			
Pre-menopause	43 (63.2)	2426 (63.2)	0.99
Post-menopause	25 (36.8)	1414 (36.8)	
Total	68	3840	
Educational level, n (%)			
Primary school or lower	11 (16.2)	606 (15.8)	0.66
Tertiary high school	6 (8.8)	414 (10.8)	
Higher education	11 (16.2)	373 (9.7)	
Unknown	20(29.4)	1892(49.3)	
Total	68	3840	
Risk factors			
Parity, n (%)			
≤1	30 (44.1)	1792 (46.7)	0.22
* 2	22 (32.3)	1125 (29.3)	
* 3	7 (10.3)	426 (11.1)	
≥4	8 (11.8)	247 (6.4)	
Unknown	1 (1.5)	250 (6.5)	
Total	68	3840	
Breastfeeding, n (%)			
Yes	33 (48.5)	2259 (58.8)	0.08
No	7 (10.3)	231 (6.0)	
Unknown	28 (41.2)	1350 (35.2)	
Total	68	3840	
Age at menopause (Mean±SD, n)	50.5±3.1, 25	49.1±4.0, 1414	0.08
Family breast cancer history, n (%)			
+	3 (9.4)	131 (3.4)	0.51
-	64 (91.1)	3640 (94.8)	
Unknown	1 (1.5)	69 (1.8)	
Total	68	3840	
BMI±SD, n (kg/m^2)	22.9±3.6, 59	23.3±3.2, 3055	0.25

BMI, body mass index; PD, Paget's disease; *The Chi-square test was performed; Unknown cases were not included in statistical analyse

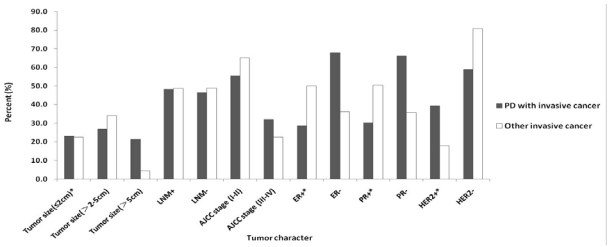

Figure 3. The Comparison of Pathologic Characters Between PD with Invasive Cancer and other Invasive Cancer. Gray bars represent the pathologic characters of mammary PD with invasive cancer. White bars represent the pathologic characters of other invasive cancer. * significant difference < 0.001. Unknown cases are not shown in the figure

significance in quadrant distribution (P < 0.001), multiple foci (P < 0.05) between the two groups. However, lateral feature was similar between the two groups (P > 0.05). Table 5 and Figure 3 showed the comparison of pathological characters between PD with underlying invasive cancer and other invasive cancer. PD with invasive breast cancer showed larger tumor size, lower ER and PR expression and higher HER2 expression than those in other invasive cancer (P < 0.001). However, the stage based on AJCC criterion showed potential difference but didn't reach statistical significance (P = 0.08). The proportion of LNM was similar in both two groups (P = 0.88). Our results indicated that PD with underlying

Table 4. Comparison in Physical Examinations Between PD with Invasive Cancer and other Invasive Cancer*

Physical examinations	PD with invasive cancer (n=56)	Other invasive cancer (n=3711)	P value
Lateral **, n (%)			
Left	29 (51.8)	1945 (52.4)	0.317
Right	26 (46.4)	1749 (47.1)	
-	1 (1.8)	17 (0.5)	
Total	56	3711	
Quadrant of focus or foci ***, n (%)			
Unifocus			
Upper-inner	5 (8.9)	615 (16.6)	<0.001
Upper-outer	19 (33.9)	1661 (44.8)	
Under-inner	3 (5.4)	214 (5.8)	
Under-outer	3 (5.4)	342 (9.2)	
Central	14 (25.0)	429 (11.5)	
Multiple foci	5 (8.9)	59 (1.6)	<0.05
Unknown	7 (12.5)	391 (10.5)	
Total	56	3711	

PD, Paget's disease; -, negative; *Unknown cases were not included in statistical analyse; **Fisher exact test were performed; ***The Chi-square test was performed

Table 5. Comparison in Pathologic Characters Between PD with Invasive Cancer and other Invasive Cancer*

Pathologic characters	PD with invasive cancer (n=56)	Other invasive cancer (n=3711)	P value
Tumor size, n (%)			
≤2cm	13 (23.2)	837 (22.6)	<0.001
≥2-5cm	15 (26.8)	1266 (34.1)	
>5cm	12 (21.4)	168 (4.5)	
Unknown	16 (28.6)	1440 (38.8)	
Total	56	3711	
LNM, n (%)			
+	27 (48.2)	1802 (48.6)	0.88
-	26 (46.4)	1812 (48.8)	
Unknown	3 (5.4)	97 (2.6)	
Total	56	3711	
AJCC Stage, n (%)			
I~II	31 (55.4)	2415 (65.1)	0.08
III~IV	18 (32.1)	834 (22.5)	
Unknown	7 (12.5)	462 (12.4)	
Total	56	3711	
ER status, n (%)			
ER+	16 (28.6)	1859 (50.1)	<0.001
ER-	38 (67.8)	1339 (36.1)	
Unknown	2 (3.6)	513 (13.8)	
Total	56	3711	
PR status, n (%)			
PR+	17 (30.3)	1875 (50.5)	<0.001
PR-	37 (66.1)	1323 (35.7)	
Unknown	2 (3.6)	513 (13.8)	
Total	56	3711	
HER2, n (%)			
HER2+	22 (39.3)	665 (17.9)	<0.001
HER2-	33 (58.9)	3001 (58.9)	
Unknown	1 (1.8)	45 (1.8)	
Total	56	3711	

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LNM, lymph node metastasis; PD, Paget's disease; PR, progesterone receptor; +, positive; -, negative; *The Chi-square test was performed; Unknown cases were not included in statistical analyse

invasive cancer may be more aggressive than those with other invasive cancer.

Discussion

PD of the nipple is a rare condition of breast cancer. The incidence is reported 0.5-5.0% of all breast cancer from different populations (Ashikari et al., 1970; Nance et al., 1970; Kothari et al., 2002; Kawase et al., 2005; Chen et al., 2006; Sukumvanich et al., 2007; Zakaria et al., 2007; Caliskan et al., 2008). The characters of PD in developed countries were well determined (Ashikari et al., 1970; Nance et al., 1970; Paone and Baker, 1981; Lagios et al., 1984; Ascenso et al., 1985; Chaudary et al., 1986; Yim et al., 1997; Adachi et al., 1998; Kollmorgen et al., 1998; Mai et al., 1999; Fu et al., 2001; Kothari et al., 2002; Kawase et al., 2005; Chen et al., 2006; Sukumvanich et al., 2007; Caliskan et al., 2008; Dalberg et al., 2008; Onoe et al., 2011). However, the characters of PD in LMCs were not determined. Only Iran and China had reported the characters of PD in LMCs (Liu et al., 2000; Wang et al., 2002; Sun et al., 2003; Yu et al., 2005; Di et al., 2007; Meibodi et al., 2008). As the health care level was different between developed countries and LMCs, these may influence the characters of PD. The previous studies from China only focus on population in northern or eastern of China and all studies are single-centered/hospital-based (Liu et al., 2000; Wang et al., 2002; Sun et al., 2003; Yu et al., 2005; Di et al., 2007). No study has been reported to characterize PD of the whole population in China. In this study, we showed the image of PD covering seven traditional districts in China from 1999 to 2008. During these ten years, the incidence and mortality of breast cancer increased rapidly (Chen and Kong, 2010; NOCPC, 2010). This research could represent the status of PD of the whole population in China today and may help to elevate the management of PD in China. As China was one of the representative LMCs, these may be also help to improve the management of PD in other LMCs.

Researches of PD in the developed countries involved demography, diagnostic imaging test, pathologic characters and clinical management. All of them were retrospective studies as PD was a rare condition. The results of these studies hinted that PD of the breast was a concomitant disease of breast cancer, showing the similar characters of demography (Ashikari et al., 1970; Nance et al., 1970; Paone and Baker, 1981; Lagios et al., 1984; Ascenso et al., 1985; Chaudary et al., 1986; Yim et al., 1997; Adachi et al., 1998; Kollmorgen et al., 1998; Fu et al., 2001; Kothari et al., 2002; Kawase et al., 2005; Chen et al., 2006; Sukumvanich et al., 2007; Zakaria et al., 2007; Caliskan et al., 2008; Dalberg et al., 2008; Onoe et al., 2011). The main pattern of PD in physical exam was patients presenting without a palpable mass in the breast. The main pattern of PD in pathologic type was PD with underlying DCIS. PD with underlying invasive cancer showed more multifocal/center, and more aggressive behavior compared with other invasive cancer, such as larger tumor size, lower ER and PR expression and higher HER2 overexpression. Based on these characters, the algorithms for the clinical management of patients with PD of the breast were proposed (Sakorafas et al., 2001). The algorithms mainly aimed at the selection of operation model in different physical exam group, which made more patients of PD take central mastectomy and segmentectomy in developed countries.

In this study, we summarized the characters of PD in China. PD of the breast was a concomitant disease of breast cancer, showing the similar characters of demography and risk factor exposure as other breast cancer (Bao et al., 2011; Li et al., 2011; Zheng et al., 2012). PD in China had some similar characters from those in the developed countries (Ashikari et al., 1970; Nance et al., 1970; Paone and Baker, 1981; Lagios et al., 1984; Ascenso et al., 1985; Chaudary et al., 1986; Yim et al., 1997; Adachi et al., 1998; Kollmorgen et al., 1998; Fu et al., 2001; Kothari et al., 2002; Kawase et al., 2005; Chen et al., 2006; Sukumvanich et al., 2007; Zakaria et al., 2007; Caliskan et al., 2008; Dalberg et al., 2008; Onoe et al., 2011). These included the percentage of PD in breast cancer, physical examination and pathologic pattern, tumor size and stage. PD with underlying invasive cancer also showed similar quadrant distribution, more multifocal/center, more aggressive behavior compared with other invasive cancer, as well as the positive rate of ER and PR.

However, PD in China showed obvious differences compared with those of the developed countries (Ashikari et al., 1970; Nance et al., 1970; Paone and Baker, 1981; Lagios et al., 1984; Ascenso et al., 1985; Chaudary et al., 1986; Yim et al., 1997; Adachi et al., 1998; Kollmorgen et al., 1998; Fu et al., 2001; Kothari et al., 2002; Kawase et al., 2005; Chen et al., 2006; Sukumvanich et al., 2007; Zakaria et al., 2007; Caliskan et al., 2008; Dalberg et al., 2008; Onoe et al., 2011). Firstly, PD in China was more common in premenopausal (63.2%) women with the mean age 48.1, which was younger than the reports from other studies (mean or median age 54-70). The proportion of patients in postmenopausal status was 36.8%, which was also lower than the reports from other studies (66.7%-83.0%). Secondly, the proportion of PD with palpable mass in physical exam (95.6%) and the proportion of PD with underlying invasive cancer (82.4%) were much higher than those found in the developed countries (15.0%-62.0% and 30.5%-66.5%, respectively). This may reflect the differences in healthcare resource level and breast cancer screening between the developed countries and China (Zheng et al., 2012). According BHGI, the diagnostic imaging resource allocation in China was in limited level, while the diagnostic image resource allocation in the developed countries was always in advanced or maximal level. The difference of the diagnostic imaging resource allocation between the developed countries and China should induce the difference in physical exam and pathologic pattern of PD. So did the lack of breast cancer screening in China. On the opposite, the developed countries took breast cancer screening for many years. Thirdly, the proportion of PD with multiple foci and HER2 overexpression were much lower in China (8.9% and 39.3% respectively) than those in the other countries (22.4%-63.0% and 79.0%-83.3% respectively). The differences in the proportion of PD

with multiple foci might reflect the difference in detection models. We detected multiple foci only by physical examinations as only 66.1% patients of mammary PD took diagnostic imaging test (Table 1). However, all the other studies in developed countries used mammography to detect multiple-foci/center disease. The difference in HER2 overexpression might due to small samples (68 cases this study vs 59-114 cases other studies), the differences of age distributions, menopause status and the difference decades of recruited patients (1999-2008 this study vs 1963-2009 other studies). The difference in recruited patients may result in the differences in the testing methodology and diagnostic criteria of biomarkers (Al-Abbadi et al., 2006; Toi et al., 2010). Otherwise the differences may also reflect the difference in risk factor exposure, genetic background among different populations (Hu et al., 2003; Ding et al., 2010; Bao et al., 2011). Therapy model of PD in China was comparatively simple (Table 1). The predominant therapy model was surgery. A lot of the patients took mastectomy, while 10.2% (7/68) patients took breast-conserving therapy. The algorithms for the clinical management of patients with PD of the breast were not proposed in China. We addressed the urgent needs for establishing the diagnostic and therapeutic guideline of Paget's disease in China as there were so many differences of PD between the developed countries and China.

There are some potential limits in this study. We selected patients from seven tertiary hospitals to represent the characters of the whole population. Selection bias may exist in the catchment of breast cancer patients in the selected hospital. These hospitals were some of the best hospitals in each district and all had the abilities of comprehensive therapy of cancer. This may reflect the levels of tertiary hospitals neither the first nor the second rank hospitals from 7 districts. As patients in China preferred to go to higher rank hospital and the first or the second rank hospitals did not have the abilities of comprehensive therapy of cancer, we thought that this may reflect the patient level of PD with breast cancer in China.

In conclusion, PD in China was a concomitant disease of breast cancer. It had an early age at diagnosis, more premenopausal status, more with invasive cancer and more likely multi-foci. The upper-outer quadrant was the most common location of PD with breast cancer, followed by center. Compared with invasive cancer, PD with invasive cancer was more likely to have larger size, ER-, PR- and HER2+, indicating the worse prognosis of PD. As mammary PD with invasive cancer was more aggressive, we address the urgent needs for establishing the diagnostic and therapeutic guideline of Paget's disease in China.

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