



Epidemiology and clinicopathologic features of breast cancer in China and the United States

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Background: Breast cancer has kept increasing since the past decades and the incidence rate is the highest among all neoplasms nowadays. China, as well as other countries, faces severe burden from the increasing population with breast cancer. This study aimed to analyze the epidemiology and clinicopathologic features of breast cancer in China and the United States (US).

Methods: Data of hospitalized patients diagnosed with primary breast cancer between 1 January 1999 and 31 December 2014 in the Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS) were reviewed. Clinical and demographic data were extracted from medical history systems, and the sixteen-year trends were analyzed. Meanwhile, retrieved data from the Surveillance, Epidemiology, and End Results (SEER) database from 1999 to 2014 were used for comparisons.

Results: A total of 18,768 breast cancer patients were included from CHCAMS, China, with 18,685 female cases (99.57%) and 81 male cases (0.43%). A total of 762,954 breast cancer patients were included from the SEER database, US, with 757,357 female cases (99.27%) and 5,597 male cases (0.73%). The peak age of breast cancer was 45–49 years old from 1999 to 2014 in China, while the peak age was 55–59 years from 1999 to 2006 and 60–64 years from 2007 to 2014 in the US. There were more young (<35 years, 6.56% *vs.* 1.97%, $P<0.001$), less elderly (≥ 65 years, 9.99% *vs.* 40.88%, $P<0.001$), less stage I (24.93% *vs.* 48.84%, $P<0.001$) and more stage III (21.00% *vs.* 12.35%, $P<0.001$) breast cancer patients in China than in the US. Patients aged 30–49 years old had a decreased trend ($P<0.001$), while 55–64 years old patients had an increased trend ($P<0.001$) from 1999 to 2014 in China, the same trend was also observed in the US. Mucinous carcinoma and histological grade I breast cancer patients increased with age both in China and the US ($P<0.001$).

Conclusions: The unique epidemiology and clinicopathologic features of breast cancer (earlier peak age, more younger patients, more advanced stage, etc.), as well as the typical trend in China, should be seriously recognized, so as to guide future prevention and management strategies.

Keywords: Breast cancer; epidemiology; clinicopathologic characteristics; China; the United States

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Introduction

Breast cancer, with an estimated 2.26 million new cases in 2020, has become the highest incidence of cancer worldwide according to the latest data reported by the International Agency for Research on Cancer (IARC) of the World Health Organization (1). Breast cancer is also a common cause of cancer death worldwide, making it a serious threat to the health of women, and a rising alarm of burden to society (2-4).

Due to the large population, cases of breast cancer in China rank number one globally, accounting for 17.6% among cases worldwide (5). As a result, breast cancer has become a non-negligible health issue and a key concern in China (6). Unfortunately, breast cancer has kept increasing since the past two decades, which may be due to the growing exposure to the risk factors: unhealthy lifestyle, low fertility rate and first full-term pregnancy at a relatively higher age, low breastfeeding rate and short breastfeeding duration, etc. (7-12).

However, there are limited cancer registries specifically for breast cancer in China and few studies examine the trends of Chinese breast cancer. It is necessary to illuminate the updated profiles and the trends of breast cancer to guide future prevention and management strategies in China. This study was a 16-year [1999–2014] retrospective clinical epidemiological study of breast cancer in China, aiming to document (I) the epidemiology, clinicopathologic characteristics and trends of Chinese breast cancer cases; (II)

the diversity of epidemiology and clinicopathologic features between China and the United States (the US). We present this article in accordance with the STROBE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2799/rc>).

Methods

Study population

Data of patients first diagnosed with primary breast cancer between 1 January 1999 and 31 December 2014 were reviewed in CHCAMS, one of the oldest and largest cancer hospitals located in the north of China. The inclusion criteria in this study were as follows: (I) patients diagnosed with primary breast cancer by pathology based on World Health Organization (WHO) criteria; (II) patients diagnosed with primary breast cancer between 1999 and 2014; (III) patients receiving treatment in the ward. Exclusion criteria were as follows: (I) patients without detailed pathology; (II) patients who were not hospitalized.

The data were collected using a survey form uniformly designed by the Epidemiology Research Office of CHCAMS. Patient characteristics (age, date of diagnosis, histological grade, pathology, site, pathological stage, residential area, etc.) were included.

For comparisons with incidents from the US, data from the corresponding period were retrieved from the SEER database, which was derived from 18 cancer registries across the US and covered about 27.8% of breast cancer cases in the US (13). Besides, breast cancer cases of Chinese from SEER in the US were also analyzed for comparison (Appendix 1).

Pathological assessment

The staging of breast cancer was based on the 1997 (5th edition), 2003 (6th edition) and 2009 UICC/AJCC (7th edition) breast cancer tumor-node-metastasis (TNM) staging standards at the diagnosed time. The histological grade and pathologic type were according to the 2003 (3rd edition) and 2012 (4th edition) WHO classification standards at the diagnosed time.

Statistical analyses

SPSS 25.0 statistical software and R Studio 3.6.4 were used for data analysis and management. Pearson Chi-square

Highlight box

Key findings

- The epidemiology and clinicopathologic characteristics of breast cancer in China were significantly different from those in the US.

What is known and what is new?

- The previous studies showed that breast cancer in China has earlier peak age and more younger patients than Westerners.
- We found that breast cancer in China has earlier peak age, more younger patients and more advanced stage than the US. Besides, we found that the younger breast cancer was decreasing, while the elder breast cancer was increasing over the period. In addition, we found that breast cancer patients with mucinous carcinoma and histological grade I increased with age both in China and the US.

What is the implication, and what should change now?

- The unique features of breast cancer in China and typical trends should be seriously recognized, so as to guide the prevention and management strategies in China.

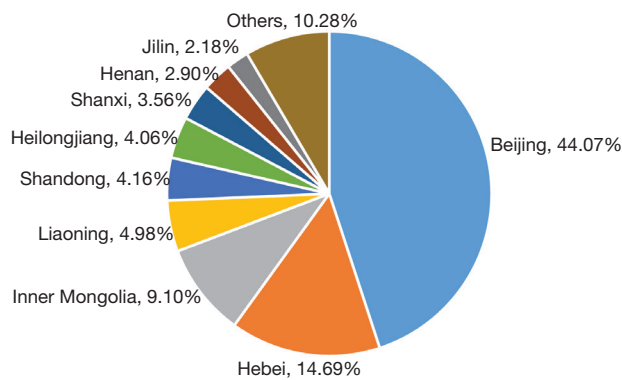


Figure 1 The distribution of breast cancer patients by province in the Cancer Hospital, Chinese Academy of Medical Sciences.

test was used to test the statistical difference between data from China and the US. Z values of the trend change for continuing data were tested by Cochran-Armitage. P values were all two-sided and P values less than 0.05 were considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (No. 15-071/998). For this was a retrospective analysis, we requested and were granted a waiver of individual informed consent from the Ethics Committee. Patient information was anonymized and protected.

Results

Patients

A total of 18,768 breast cancer patients were included in the study. Among 18,768 breast cancer patients, 18,685 cases were female (99.57%) and 81 were male cases (0.43%). *Figure 1* presents the distribution of female breast cancer patients by province: 8,235 cases were from Beijing (44.07%), 2,745 from Hebei (14.69%), 1,701 from Inner Mongolia (9.10%), 931 from Liaoning (4.98%), 777 from Shandong (4.16%), 759 from Heilongjiang (4.06%), 666 from Shanxi (3.56%), 542 from Henan (2.90%), 408 from Jilin (2.18%), and 1,921 (10.28%) from other areas.

There were 762,954 cases in the SEER database, including 757,357 cases of female breast cancer (99.27%) and 5,597 male cases (0.73%).

Comparison of epidemiology and clinicopathologic features of female breast cancer patients in China and in the US

Compared with the US, female breast cancer in China was statistically different in age ($P < 0.001$), stage ($P < 0.001$), histological grade ($P < 0.001$), and location ($P < 0.001$). There were more young breast cancers (<35 years old) (6.56% vs. 1.97%, $P < 0.001$), yet fewer elderly breast cancers (≥ 65 years old) in China than in the US (9.99% vs. 40.88%, $P < 0.001$). Patients with stage I were significantly fewer (24.93% vs. 48.84%, $P < 0.001$) in China than in the US. However, there were more patients with stage III breast cancer in China than in the US (21.00% vs. 12.35%, $P < 0.001$). The proportion of patients with histological grade I breast cancer in China was lower than that in the US (6.15% vs. 21.63%, $P < 0.001$), but the proportion of patients with grade II in China was higher than in the US (63.21% vs. 41.92%, $P < 0.001$). Compared with the US, patients were more likely to have upper breast cancer (51.85% vs. 44.19%, $P < 0.001$) and central breast cancers (20.02% vs. 5.77%, $P < 0.001$) in China. *Table 1* illustrates the details.

The trend of female breast cancer in epidemiology and clinicopathologic characteristics in China and in the US

As shown in *Figure 2A*, the distribution graph of the age of female breast cancer is like an inverted “V” in China. The peak incident age was 45–49 years old in 1999–2014. The proportion of patients aged 55–64 years increased through the study (55–59 years, $Z = 9.03$, $P < 0.001$; 60–64 years, $Z = 5.10$, $P < 0.001$), along with the decreasing trend for the patients aged 30–49 years (30–34 years, $Z = -4.35$, $P < 0.001$; 35–39 years, $Z = -5.08$, $P < 0.001$; 40–44 years; $Z = -3.96$, $P < 0.001$; 45–49 years, $Z = -4.78$, $P < 0.001$). The peak age in the US increased from 55–59 years in 1999–2006 to 60–64 years in 2007–2014, and there was a trend of older age for the first diagnosis (*Figure 2B*).

The proportion of stage II cancer patients decreased from 56.01% in 1999–2002 to 38.81% in 2011–2014 ($Z = -12.11$, $P < 0.001$) in China, while the proportion of stage IV patients increased from 3.03% to 9.86% ($Z = 8.22$, $P < 0.001$) (*Figure 3A*). Whereas in the US, the proportion of stage I and stage II cancer patients increased ($Z = 4.75$, $P < 0.001$; $Z = 5.58$, $P < 0.001$), and stage III decreased

Table 1 Comparison of clinicopathological features of female breast cancer patients in China and the United States

Characteristics	China, n (%)	The United States, n (%)	χ^2	P value
Total	18,685 (100.0)	757,357 (100.0)		
Age at diagnosis* (years)			12,533.80	<0.001
<35	1,214 (6.56)	14,931 (1.97)		
35–44	4,912 (26.56)	76,338 (10.01)		
45–54	6,586 (35.62)	167,286 (21.93)		
55–64	3,915 (21.17)	186,892 (24.50)		
65–74	1,470 (7.85)	161,051 (21.11)		
≥75	395 (2.14)	150,859 (19.77)		
Pathological type			1,341.81	<0.001
Invasive ductal	16,966 (90.80)	622,843 (82.24)		
Invasive lobular	488 (2.61)	75,807 (10.01)		
Invasive mucinous	364 (1.95)	19,474 (2.57)		
Invasive medullary	183 (0.98)	3,607 (0.48)		
Others	684 (3.66)	35,626 (4.70)		
Stage*			1,733.60	<0.001
I	1,824 (24.93)	349,194 (48.84)		
II	3,392 (46.36)	242,450 (33.91)		
III	1,536 (21.00)	88,301 (12.35)		
IV	564 (7.71)	34,977 (4.89)		
Histological grade*			3,079.28	<0.001
Grade I	844 (6.15)	150,336 (21.63)		
Grade II	8,677 (63.21)	291,284 (41.92)		
Grade III	4,207 (30.64)	253,263 (36.45)		
Surgery			4,610.77	<0.001
Yes	14,715 (78.75)	699,536 (92.37)		
No	3,970 (21.25)	57,821 (7.63)		
Chemotherapy			4,315.86	<0.001
Yes	2,957 (15.83)	299,552 (39.55)		
No	15,728 (84.17)	457,805 (60.45)		
Radiotherapy			11,816.12	<0.001
Yes	837 (4.48)	336,100 (44.38)		
No	17,848 (95.52)	421,257 (55.62)		
Location			8,846.35	<0.001
Upper	9,674 (51.77)	334,709 (44.19)		
Central	3,741 (20.02)	43,678 (5.77)		
Lower	2,474 (13.24)	93,550 (12.35)		
Others	2,796 (14.96)	285,420 (37.69)		

*, some information was unknown.

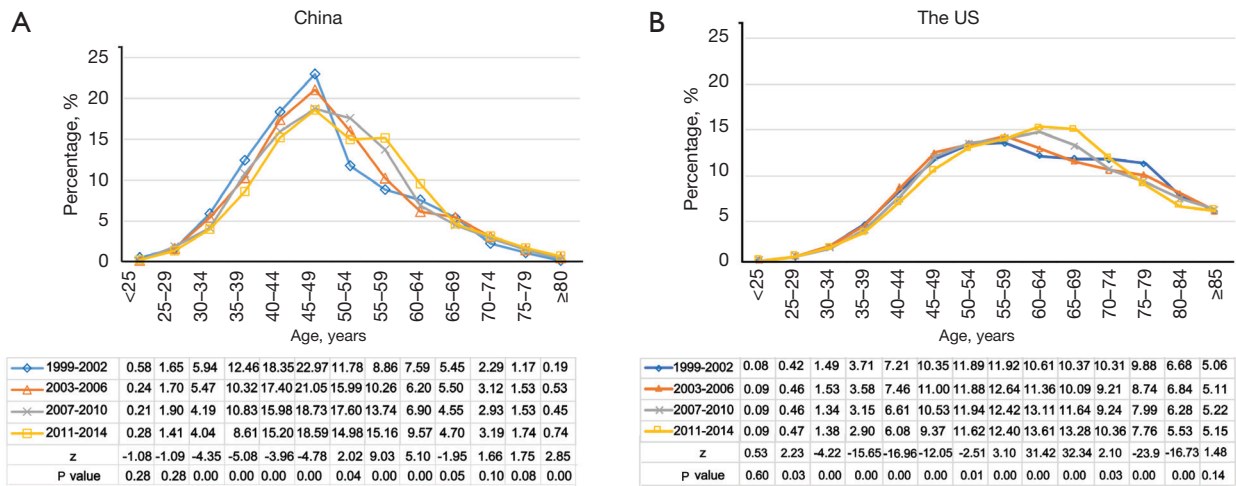


Figure 2 The age distribution graph and changes of female breast cancer in 1999–2014. (A) China; (B) the United States.

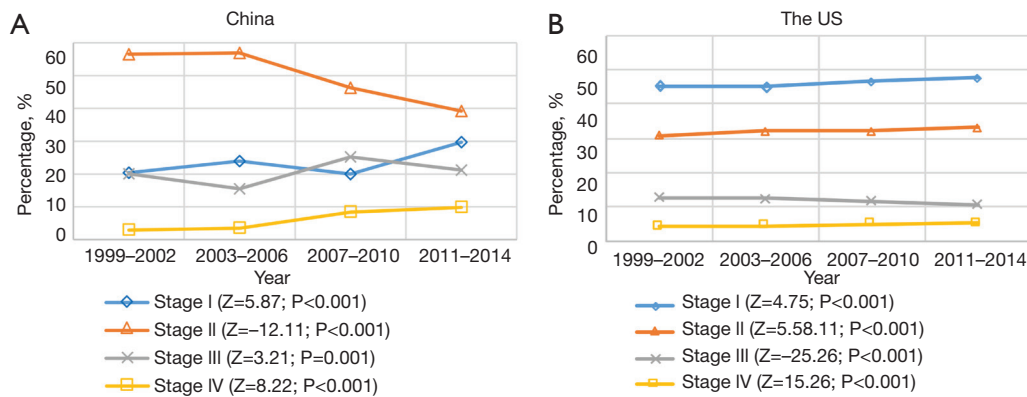


Figure 3 The staging and changes of female breast cancer in 1999–2014. (A) China; (B) the United States.

($Z=-25.26, P<0.001$) (Figure 3B).

Overall, the most frequent histological type of breast cancer was ductal carcinoma. Figure 4 shows the trend of the four main histological types of breast cancer in 1999–2014. Increased trend of ductal carcinoma ($Z=4.16, P<0.001$), decreased trend of lobular carcinoma ($Z=-6.58, P<0.001$) and medullary carcinoma ($Z=-8.87, P<0.001$) were observed in China from 1999 to 2014. Ductal carcinoma and lobular carcinoma increased in the US, while medullary carcinoma and mucinous carcinoma decreased over the period (Figure 4B).

The change of clinicopathologic characteristics of breast cancer by age in China and in the US

The association between different characteristics (stage, grade, pathology) and age was investigated in the study.

Over the period from 1999 to 2014, the patients with stage I showed an increased trend by age both in China and in the US ($Z=2.88, P=0.004; Z=94.95, P<0.001$), while patients with stage III decreased ($Z=-2.36, P=0.018; Z=-59.05, P<0.001$) (Figure 5A, 5B). The patients with grade I elevated significantly with the increasing of age both in China and in the US ($Z=3.56, P<0.001; Z=86.73, P<0.001$) (Figure 6A, 6B). A similar increased trend by age was also found for mucinous carcinoma ($Z=1.99, P=0.046; Z=63.30, P<0.001; Z=67.43, P<0.001$). Whereas medullary carcinoma decreased with the increasing of age both in China and in the US ($Z=-3.61, P<0.001; Z=-34.17, P<0.001$). The proportion of patients receiving radiotherapy and chemotherapy in China was relatively lower when compared with those in the US (Table 1). Patients that received

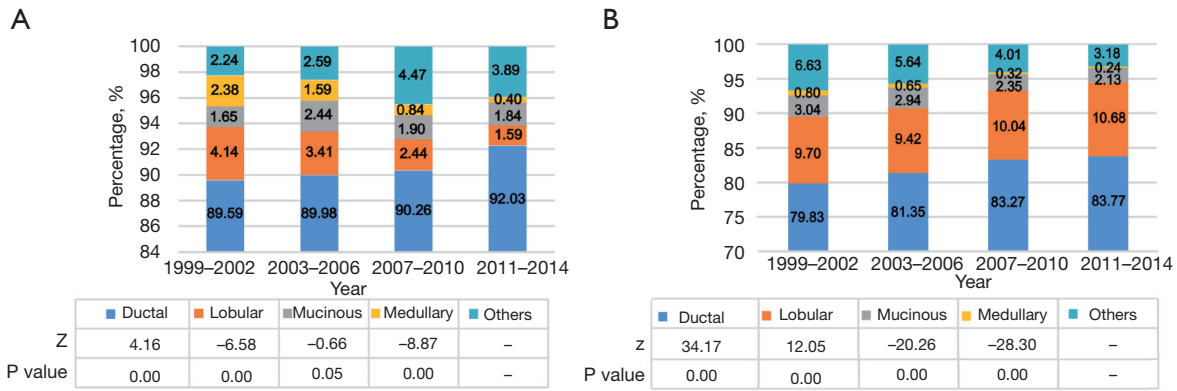


Figure 4 The histological types and changes of female breast cancer in 1999–2014. (A) China; (B) the United States.

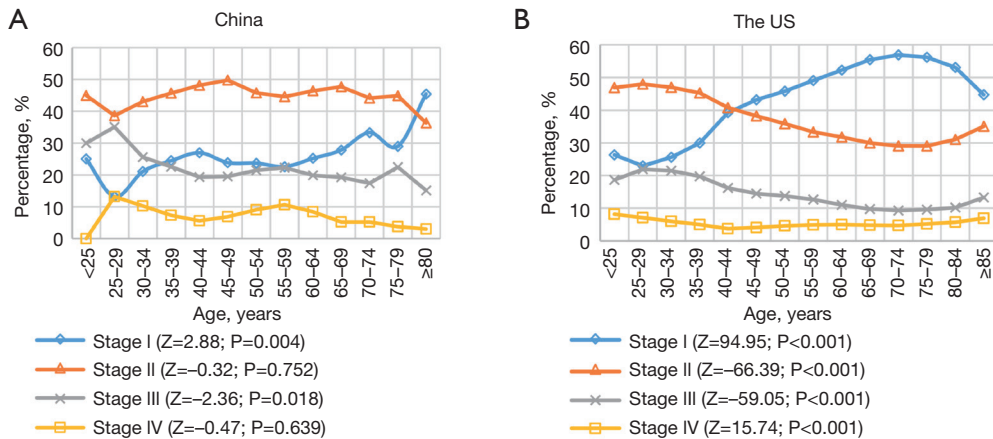


Figure 5 The staging changes with age of female breast cancer. (A) China; (B) the United States.

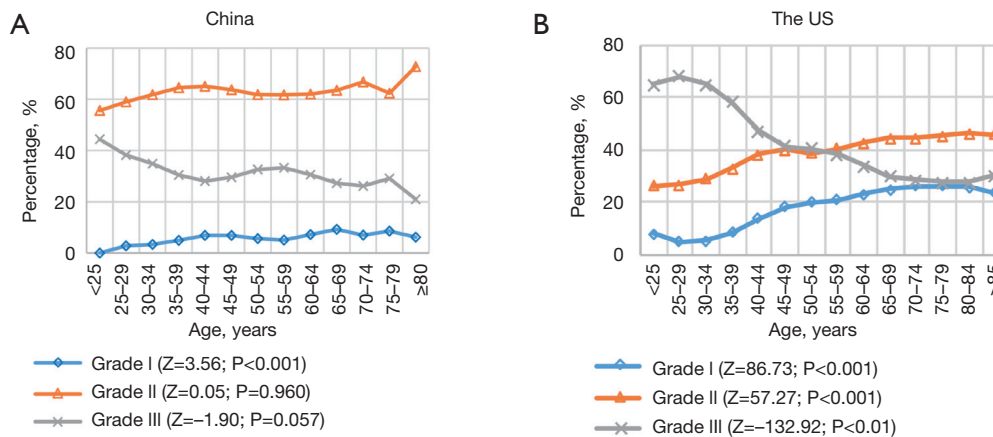


Figure 6 The histological grading and changes with age of female breast cancer. (A) China; (B) the United States.

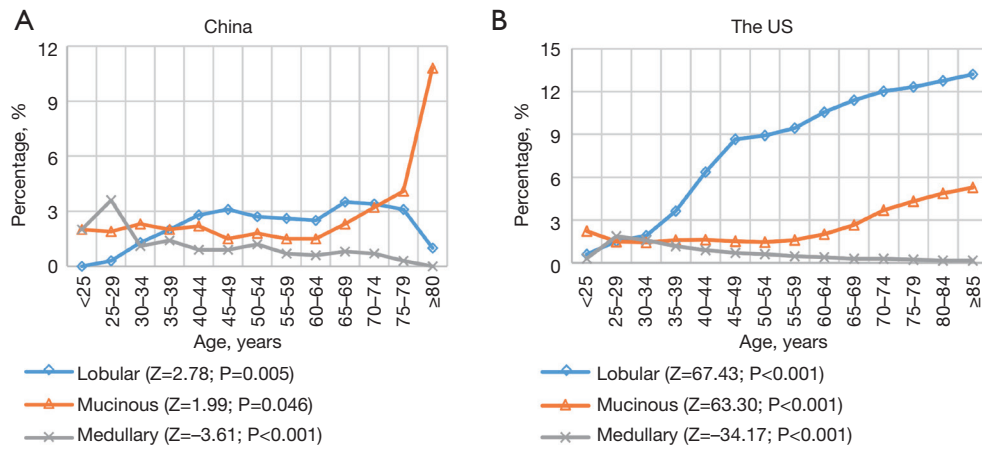


Figure 7 The histological type changes with age of female breast cancer. (A) China; (B) the United States.

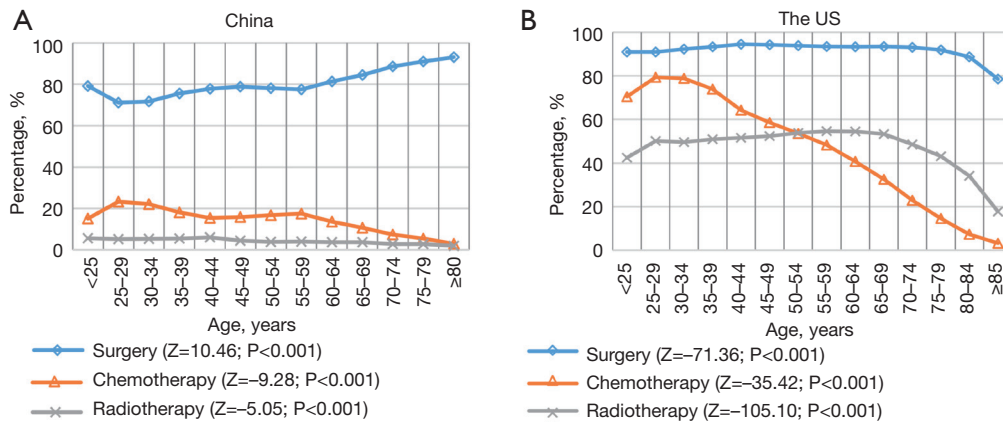


Figure 8 The treatment changes with age of female breast cancer. (A) China; (B) the United States.

radiotherapy and chemotherapy decreased sharply with the increasing of age both in China and the US (Figure 8A, 8B).

Discussion

In this study, a large cohort of breast cancer patients diagnosed at CHCAMS from 1999–2014 was included. The data showed that the epidemiology and clinical characteristics of breast cancer in China are significantly different from those in the US: earlier peak age, more younger patients, and more advanced stage. The trends of breast cancer both in China and the US during the study period were also analyzed.

In the study, the peak age of breast cancer at diagnosis was 45–49 years old in China, which was consistent with the observations from previous studies and showed 10 years

earlier of onset age than the Western populations (14–16). Li and colleagues showed that the mean age at diagnosis and age range of breast cancer patients in China was 48.7 years (standard deviation =10.5 years) from 1999 to 2008 (17). Fan *et al.* found that the peak age of breast cancer increased from 47.5 years in 1990 to 50 years in 2007 in Shanghai (18). Besides, this current study found that the 55–64 years old patients had an increased trend (P<0.001) from 1999 to 2014 in China, the same trend was also observed in the US. This may be explained by two reasons (19). First, an aging population with more elderly is observed in recent decades. Second, a growing number of people are in connection with the exposure to the risk factors of breast cancer.

This current study showed that the proportion of early-stage (stage I & II) breast cancer in China was much lower than that in the US, which may be due to the absence of a

nationwide screening program for breast cancer in China. China is a developing country with a large population, nationwide breast cancer screening program is difficult to be conducted. Previous evidence suggested that breast cancer screening can improve the early diagnosis rate and reduce the mortality rate (20). There was a strong association between patient delay and stage at diagnosis in breast cancer, especially for poorly differentiated tumors (21). 29–36% patient delay of diagnosis for breast cancer was observed in China (22). Mammography is usually used to screen for early breast cancer in the US (23), which may be not suitable for Chinese society. A previous study found that the breast of Chinese women was smaller and more compact than that of Westerners, demonstrating that ultrasound combined with mammography may be the optimal screening method for Chinese (24). Though several screening projects for breast cancer have been initiated by the government in China, there is still a long way to go.

In this study, the proportion of young breast cancer patients (<35 years old) in China was higher than that in the US. Kan and colleagues found that Asian breast cancer patients were associated with increased tumor-infiltrating lymphocytes (TILs) and decreased transforming growth factor- β (TGF- β) signaling expression, indicating that younger Asian breast cancer patients have more immune-active microenvironment than westerners (25). The research of Han *et al.* suggested that young breast cancer was 7.78% during 2000–2015 in Beijing and had no obvious change over the period (26). However, this current study found that there was a decreasing trend of 30–34 years young breast cancer patients in China over the period. The difference between the two studies may be due to the fact that the incidence of young breast cancer is relatively low among the whole group, and different populations have biases. This deserves further investigation with large-scale multi-center research.

The proportion of elder breast cancer patients aged ≥ 65 years in China were lower than that in the US. Nevertheless, the number of elder patients has been gradually increased in recent years both in China and the US. This current study found that the pathological features of elder breast cancer were more indolent than that of younger breast cancer. Breast cancer in elder age were more likely to be mucinous carcinoma, grade I histology, and early stage (27). But that does not imply that elderly breast cancer patients can be free from chemotherapy and radiotherapy (28). The International Society of Geriatric Oncology (SIOG) guidelines recommend elderly cancer

patients undergoing comprehensive geriatric assessment (CGA) routinely and receiving guideline-recommended therapy according to CGA scores (29). More attention should be paid to elderly patients and further investigations are required among elderly patients with breast cancer in the near future.

This study included a large number of breast cancer cases covering a long period time, which facilitated an extensive assessment of the epidemiology and clinicopathologic characteristics of breast cancer patients in China. By comparing with corresponding data from the US, it raised consciousness for unmet medical care and management across China. However, this study also had several limitations. First, this study was based on hospital inpatient records instead of the whole population, data quality was mainly dependent on the documentation of the clinicians. Second, survival data was absence in this study. Third, breast cancer patients in 1999–2014 in China were from a single Cancer Hospital in Beijing, in which the cases came from many different provinces. whereas breast cancer cases in SEER in the US were from the population-based cancer registries (18 SEER areas) which included many cases from hospital inpatients, outpatients, and communities. This may lead to bias and relatively a little higher stage cancer cases in China.

Conclusions

The epidemiology and clinicopathologic characteristics of breast cancer in China were significantly different from those in the US: earlier peak age, more younger patients, more advanced stage, etc. Besides, the trend analysis showed that the younger breast cancer was decreasing, while the elder breast cancer was increasing over the period. The unique features of breast cancer in China and typical trends should be seriously recognized, so as to guide the prevention and management strategies in the future in China. In addition, working out an online information database that provides scientific and effective records, will play a crucial role in the prevention and treatment of breast cancer in China.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2799/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (No. 15-071/998). For this was a retrospective analysis, we requested and were granted a waiver of individual informed consent from the Ethics Committee. Patient information was anonymized and protected.

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Appendix 1 Epidemiology and clinicopathologic features of breast cancer in China and the United States

There were 9,462 cases of Chinese in the SEER database, including 9,417 cases of female breast cancer (99.52%) and 45 male cases (0.48%). The peak incident age was 45–54 years old in 1999–2014 for Chinese in the SEER database. The young breast cancer (<35 years old) of Chinese in the SEER database were fewer than those in China (6.56% *vs.* 2.50%), but more than the in the US (2.50% *vs.* 1.97%). The elderly breast cancer (≥ 65 years old) of Chinese in the SEER database were more than those in China (30.72% *vs.* 9.99%), but fewer than those in the US (30.72% *vs.* 40.88%). Patients with stage I of Chinese in the SEER database were more (24.93% *vs.* 48.84%) than those in China, but were the same with the US (50.15% *vs.* 48.84%).

Table S1 Comparison of clinicopathological features of female breast cancer patients in China, the Chinese population in the United States and the United States

Characteristics	China, n (%)	The Chinese population in the United States, n (%)	The United States, n (%)	χ^2	P value
Total	18,685 (100.0)	9,417 (100.0)	757,357 (100.0)		
Age at diagnosis*				13,119.95	<0.001
<35 years	1,214 (6.56)	235 (2.50)	14,931 (1.97)		
35–44 years	4,912 (26.56)	1,397 (14.83)	76,338 (10.01)		
45–54 years	6,586 (35.62)	2,753 (29.23)	167,286 (21.93)		
55–64 years	3,915 (21.17)	2,139 (22.71)	186,892 (24.50)		
65–74 years	1,470 (7.85)	1,571 (16.68)	161,051 (21.11)		
≥ 75 years	395 (2.14)	1,322 (14.04)	150,859 (19.77)		
Pathological type				1,765.08	<0.001
Invasive ductal	16,966 (90.8)	7,950 (84.42)	622,843 (82.24)		
Invasive lobular	488 (2.61)	438 (4.65)	75,807 (10.01)		
Invasive mucinous	364 (1.95)	343 (3.64)	19,474 (2.57)		
Invasive medullary	183 (0.98)	27 (0.29)	3,607 (0.48)		
Others	684 (3.66)	659 (7.00)	35,626 (4.7)		
Stage *				1,797.45	<0.001
I	1,824 (24.93)	4,441 (50.15)	349,194 (48.84)		
II	3,392 (46.36)	3,145 (35.51)	242,450 (33.91)		
III	1,536 (21.00)	958 (10.82)	88,301 (12.35)		
IV	564 (7.71)	312 (3.52)	34,977 (4.89)		
Histological grade*				3,095.73	<0.001
Grade I	844 (6.15)	1,725 (20.40)	150,336 (21.63)		
Grade II	8,677 (63.21)	3,765 (44.52)	291,284 (41.92)		
Grade III	4,207 (30.64)	2,967 (35.08)	253,263 (36.45)		
Surgery				4,653.58	<0.001
Yes	14,715 (78.75)	8,818 (93.64)	699,536 (92.37)		
No	3,970 (21.25)	599 (6.36)	57,821 (7.63)		
Chemotherapy				4,327.62	<0.001
Yes	2,957 (15.83)	3,840 (40.78)	299,552 (39.55)		
No	15,728 (84.17)	5,577(59.22)	457,805 (60.45)		
Radiotherapy				11,825.18	<0.001
Yes	837 (4.48)	4,244(45.07)	336,100 (44.38)		
No	17,848 (95.52)	5,173 (54.93)	421,257 (55.62)		
location				8,846.17	<0.001
Upper	9,674 (51.85)	4,199 (44.59)	334,709 (44.19)		
Central	3,741 (20.05)	576 (6.12)	43,678 (5.77)		
Lower	2,474 (13.26)	1,145 (12.16)	93,550 (12.35)		
Others	2,796 (14.99)	3,497 (37.13)	285,420 (37.69)		

*, some information was unknown.