RESEARCH ARTICLE

Age of Diagnosis of Breast Cancer in China: Almost 10 Years Earlier than in the United States and the European Union

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Abstract

Background: The study aimed to describe the age distribution of breast cancer diagnosis among Chinese females for comparison with the United States and the European Union, and provide evidence for the screening target population in China. Materials and Methods: Median age was estimated from hospital databases from 7 tertiary hospitals in China. Population-based data in China, United States and European Union was extracted from the National Central Cancer Registry, SEER program and GLOBOCAN 2008, respectively. Age-standardized distribution of breast cancer at diagnosis in the 3 areas was estimated based on the World Standard Population 2000. Results: The median age of breast cancer at diagnosis was around 50 in China, nearly 10 years earlier than United States and European Union. The diagnosis age in China did not vary between subgroups of calendar year, region and pathological characteristics. With adjustment for population structure, median age of breast cancer at diagnosis was 50~54 in China, but 55~59 in United States and European Union. Conclusions: The median diagnosis age of female breast cancer is much earlier in China than in the United States and the European Union pointing to racial differences in genetics and lifestyle. Screening programs should start at an earlier age for Chinese women and age disparities between Chinese and Western women warrant further studies.

Keywords: Breast cancer - onset age - racial/ethnic variation - China - United States and European Union

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Introduction

Breast cancer (BC) is the most frequent female cancer worldwide and the new cases accounted for 23% of all female cancers in 2008 (Ferlay et al., 2008), ranking second overall (Ferlay et al., 2008). China is the country having severe burden of cancers worldwide, with the occurrence of 22% all cancers and 12% BC (Ferlay et al., 2008). In China, breast, lung and stomach cancers are the most frequent cancers among females, the incidences all >20/105 (Ferlay et al., 2008). Female BC in China had an increasing trend reported from registry data (Wu et al., 2014).

BC has a remark ethnic variation in incidence. In the United States (US), incidence of BC was 95/105 among Asian-American women, much lower than white women of 127/105 (Howlader et al., 2012). Asian women generally have low BC incidence at their native countries, but face to a rapid increase after the immigration to the US (Deapen et al., 2002). The changing lifestyle environment might play an important role in the incidence increase. Age of BC at diagnosis was also different between races potentially. In SEERs, median age of BC patients at diagnosis was 62 among White females and 58 among Black females (Howlader et al., 2012). The race variation of age at diagnosis was also observed between Non-Hispanic whites, Blacks, Hispanic white and Asian women, residing in US and Sweden (Kurian et al., 2010; Hemminki et al., 2011; Yi et al., 2012). The racial difference occurred in Asia too: Hong Kong Chinese women presented an earlier age of BC at diagnosis than the Caucasians from US (Kwong et al., 2008). Currently, the US and some European Union (EU) countries have already initiated the nationwide screening program and

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covered the women aged more than 40. China is at the starting point for the nationwide screening program. Age had a significant effect on the diagnosis efficacy for female BC in China (Wang et al., 2013). For the evidence of starting age in screening, this study integrated both the hospital-based and population-based databases to describe the age at diagnosis of breast cancer native in China and compare with US and EU.

Materials and Methods

Study design

Both hospital-based and population-based databases were introduced for the analyses in Chinese female cases: the hospital-based database was a 10-year retrospective multi-center female breast cancer study (Li et al., 2010; Zheng et al., 2012), recruiting female breast cancer patients from 7 tertiary hospitals at 7 classic geographic regions during 1999~2008; the population-based database was from National Central Cancer Registry 2008 database which had 95 Cancer Registry units across China. Female BC data of US was from Surveillance, Epidemiology and End Results (SEER) 2005-2009 database (Howlader et al., 2012) and EU data was from GLOBOCAN 2008 database (Ferlay et al., 2008).

Study patients

In the multi-center study, the 7 hospitals were chose from Beijing, Guangzhou, Hangzhou, Shenyang, Changsha, Xi'an and Chengdu from 1999 to 2008, and in 1999, the particular month was selected randomly to represent the whole year and the patients recruited into hospital that month were included in the study, in 2000, the patients recruited into the hospital at the next month were included into the study etc. For example, if the patients at March 1999 were chose in 1999, the patients at April 2000 were chose in 2000. The detailed description was reported in previous studies (Li et al., 2010; Zheng et al., 2012). The inclusion criteria for the patients were as follows: (1) primary breast cancer with pathological evidence; (2) the admission date was in the study period; (3) receiving or received any forms of therapies. In each selected month, if inpatients admissions were less than 50, more cases were enrolled from the neighboring months until the total number in that year reaching 50. If inpatients number in the selected month exceeded 50, all cases should be reviewed. This was approved by the Cancer Foundation of China Institutional Review Board. All the interested data was collected from the medical records and during the 10-year observation, some of the patients have died. The institutional review board waived the need for written informed consent from the participants, but the informed consents were obtained from participated hospitals.

In SEER and GLOBOCAN 2008 databases, data of age-specific incidence and age distribution of female BC patients from US and EU were selected for comparison with Chinese female BC patients.

Data collection

Data collection was conducted under the approved procedures. The collected data included demographic factors, risk factors, pathological characteristics, lymph node metastasis (LNM) and tumor size. Pathological type was referred to 1981 and 2003 WHO histological classification criterion (Tavassoli and Devilee, 2003; Ingelman-Sundberg, 2004). The classification of BC stage was based on the criteria by American Joint Committee on Cancer (AJCC) (American Joint Committee on Cancer, 1997; American Joint Committee on Cancer, 2002). The expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) was detected via immunohistochemistry. In this study HER2+ meant overexpression of HER2 with score of 3+ and HER- was the status of HER2 of lower score (Zarbo and Hammond, 2003). The expression of ER or PR and HER2 defined the four molecular subtypes of BC: luminal A (ER+ or PR+ and HER2-), luminal B (ER+ or PR+ and HER2+), triple negative (TNBC) (ER-/PR- and HER2-), and HER2 positive (HER2+) (ER-/PR-and HER2+) (Caldarella et al., 2011).

Statistical analysis

In hospital-based database, the age of BC at diagnosis was described by median, 25% and 75% percentile. The age distribution of female BC cases was estimated in Chinese, US and EU populations, by dividing the age-specific cases to total number, respectively. The age-standardized distribution of female breast cancer cases was calculated by direct standardization with the reference of BC incidences from population databases in China, US (Howlader et al., 2012) and EU (Ferlay et al., 2008) and the world standard population in 2000 (Ahmad et al., 2001): that multiplying age-specific incidence with particular standard population and then estimating the age distribution individually.

Results

Medical records of 4211 eligible patients were selected from 45200 ones. Median age at diagnosis was 48 for total patients (Table 1). From 1999 to 2008, the median age was under 50 years old and changed from 45 to 49. Though the 7 selected regions had socioeconomic disparities, median age at diagnosis did not change too much, ranging 46 to 49 (Table 1).

The diagnosis age was the same between BC stages with the median of 48 (Table 2). Median age at diagnosis in pathological types ranged from 46 to 48 and in the cases with BC in-situ was 46.5 years of age (Table 2). The molecular subtypes of BC had a 3 year-variation in median age at diagnosis, ranging from 47 to 50 (Table 2). The BC patients with various statues of lymph metastasis and tumor size had similar age at diagnosis, from 47 to 48 (Table 2).

Population-based database from National Central Cancer Registry presented the median age of breast cancer at diagnosis was 53 years age in China. BC cases distributed in double direction with age groups, first increase and then decrease (Figure 1). In the hospital-based database, the percentage of BC cases younger than 50 years old was higher the population-based database from National Central Cancer Registry (Figure 1).

Table 1. Age at BC Diagnosis among Females in China from 1999 to 2008

	N	Median age	25% percentile	75% percentile
Total	4211	48	41	55
Year				
1999	403	45	40	52
2000	349	46	41	54
2001	377	47	41	54
2002	341	47	40	54
2003	390	48	40	55
2004	417	48	41	54
2005	406	47	41	53
2006	462	48	42	55
2007	567	49	42	55
2008	496	49	42	56
Region				
Beijing	641	49	42	56
Shenyang	832	48	42	54.5
Changsha	546	47	41	54
Guangzhou	603	47	40	54
Hangzhou	604	46	40	52
Xi'an	483	48	42	56
Chengdu	499	47	41	55

Table 2. Age at Diagnosis and Pathological Status

	N	Median age	25% percentile	75% percentile
Stage				
I	662	48	42	56
II	1889	48	42	55
III	788	48	41	55
IV	113	48	41	54
Pathological Type				
In-situ	136	46.5	40.5	54
Ductal	3470	48	41	55
Lobular	135	46	41	54
Others	248	48	40	56
Molecular subtype				
Triple negative	733	48	41	55
HER2+	285	50	43	56
Luminal A	1749	48	41	55
Luminal B	446	47	41	54
LNM				
0	1989	48	41	55
1~3	1036	47	41	54
>=4	922	48	41	54
Size				
<=2 cm	1072	47	41	55
<=5 cm	2095	48	42	56
>5cm	410	47	41	54

HER2, human epidermalgrowth factor receptor-2; LNM, lymph node metastasis

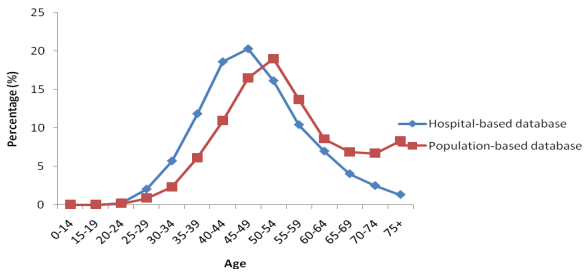

Figure 1. Age Distribution (%) of Female Breast Cancer at Diagnosis in China*. *Hospital-based database from multi-center epidemiological study, population-based database from National Central Cancer Registry

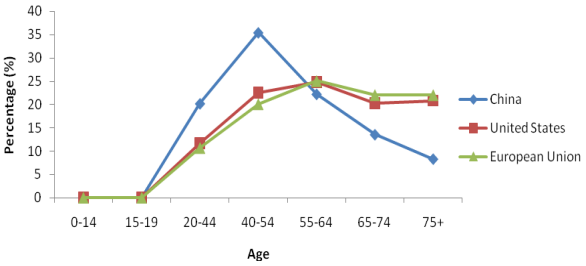

Figure 2. Age Distribution (%) of Female Breast Cancer at Diagnosis in China, US and EU*. *population-based databases for China, US and EU were from National Central Cancer Registry 2008, SEER program 2005-2009 and GLOBOCAN 2008, respectively

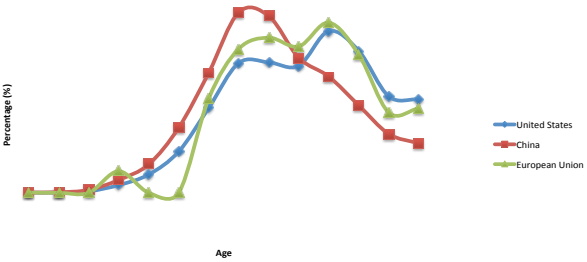

Figure 3. Age-Standardized Distribution of Female Breast Cancer at Diagnosis in China, US and EU*. *world standard population of 2000 used for standardization; population-based databases for China, US and EU were from National Central Cancer Registry 2008, SEER program 2005-2009 and GLOBOCAN 2008, respectively

In figure 2, the median age at diagnosis was 50~54 in the population-based database but in SEER and GLOBOCAN 2008, the median age for BC at diagnosis was 60~64, a 10-year difference between China and Western females (Figure 2). In the population-based databases, the percentage of BC cases diagnosed less than 60 years old in China was 70%, much higher than US (46%) and EU (43%). The proportion of cases at diagnosis younger than 50 years old was 37% in China, the corresponding figure in US and EU were 23%. With the age standardization by world standard population of 2000, BC cases in the 3 regions all distributed in double direction mode with age (Figure 3). However, the peak proportion appeared in the 45~49 age group in China, nearly 15 years younger than US and EU (Figure 3). With the adjustment of population structure, the median age at diagnosis was in the age group of 50~54 in China, but 55~59 in US and EU, still a 5-year difference (Figure 3).

Discussion

This study integrated both of the hospital-based and population-based databases together, presented and compared the age at diagnosis between geographic regions, calendar years and pathological subgroups. The age at diagnosis estimated from National Central Cancer Registry was compared with US and EU. Median age of female BC patients at diagnosis was around 50 years old and did not have significant variation between regions, year, stage, pathological types and subtypes. Compared

with the cases from US and EU, Chinese female BC patients were 10 years earlier at diagnosis. With the consideration of difference in population structure, there was still a 5-year interval between China and Western countries.

From the SEER database, median age of female BC at diagnosis was 61.0 among females (Howlader et al., 2012), 8 years older than Chinese women. The earlier age at diagnosis in Chinese female BC cases was also reported from some other studies. In Hong Kong, the median age of Chinese female patients was less than 50, much younger than the Chinese and Caucasian women residing in US (Kwong et al., 2008). Asian-American women presented BC at 56, 7 years younger than the Non-Hispanic White women in US (Kurian et al., 2010; Yi et al., 2012). Asian immigrants in Sweden also reported the younger age than native women (Hemminki et al., 2011). Asian women were diagnosed for BC, younger than Western women. This study standardized the different population structure between China, US and EU, and presented the similar result from hospital and population-based database, Chinese women presenting BC nearly 10 years younger than Western women clinically.

From SEER database, the stage of BC in Asian-American women was more advanced than Non-Hispanic White women (Ooi et al., 2011), and the Chinese native cases had more in advanced stage than US and Europe (Zheng et al., 2012). US and EU have already initiated the national screening program, which aims to capture the BC in situ and in earlier stage, while in China, the nationwide screening program has not been initiated. The perception of BC prevention among US and EU women was much more prevalent than Chinese women. These factors might contribute to the more Chinese female cases in advanced stages at diagnosis than Western countries. Surprisingly, in common sense lack of screening program should reduce the possibility of early age at clinical diagnosis. Though no nationwide screening has been carried out in China, the median age of BC at diagnosis is still 8 years earlier than in US and EU. Even the median age of BC in situ from China (Table 2) was more than 10 years older the in situ cases from US (Howlader et al., 2012). The racial difference of age at diagnosis was possible from variated characteristics in genetics and risk factor exposures, rather than the initiation of screening action. Besides of the age difference, the incidence of BC had a racial/ethnic disparities : From the population-based cancer registry center at Los Angles County, the age-standardized incidence of BC among Asian-American women had an increasing trend (Liu et al., 2012; Deapen et al., 2002) but the incidence among the Non-Hispanic White, Black and Hispanic women was in a reducing trend (Liu et al., 2012), and age-specific incidence increased with age in the Non-Hispanic White, Black and Hispanic women but increased to a peak at 55 years of age and then decreased in Chinese, Pilipina, Japanese and Korean women (Liu et al., 2012). The phenomenon was similar as this result (Figure 2, 3). The disparities in BC diagnosis age and incidence might suggest a significant difference of background characteristics between Asian and Western women. And with age standardization account for the population structure difference, the Chinese female cases were diagnosed 5 years earlier than US and EU, indicating the racial/ethnic difference between China and Western countries (Figure 3).

In our previous paper, Chinese female BC patients had more aggressive features in pathology than US and European women (Zheng et al., 2012) that larger tumor size, higher proportion of invasive ductal carcinoma, lower proportion in early stage, lower proportion of positive ER, lower proportion of positive PR and higher proportion of HER2+. Additionally, molecular subtypes including luminal A, luminal B, HER2+ and triple negative BC had racial disparities between Asian and Western women (Kurian et al., 2010; Telli et al., 2011). The pathological variation might be induced by the unequal background characteristics between races.

Compared with Non-Hispanic White women, the risk of BC was lower by more than 50% among Chinese women at Los Angles County (Liu et al., 2012), indicating the racial variation in the cancer risk, both genetic and environmental risk factors. The polymorphic gene variants related with insulin like growth factor-1 and estrogen metabolism had different distribution between White and Asian women (Jernstrom et al., 2001). BRCA1 mutations were more common among US White women while BRCA2 mutations were more common among Asian women (de Bruin et al., 2011) and the risk-associated alleles in MAP3K1 and TOX3/TNRC9 were more common in Asian women too (de Bruin et al., 2011).

More Chinese BC patients occurred at working age, in contrast with US and EU. China is more interested to develop labor intensive industries which might introduce higher occupational exposures for BC risk. The working age introduced occupational exposure to some risk factors which was possible to increase BC risk, such as less sleep duration (Thompson and Li, 2012), night shift work (Hansen and Lassen, 2012) and exposure of exogenous environmental chemicals (Manuwald et al., 2012; Villeneuve et al., 2010; Brody and Rudel, 2003). The exogenous chemicals might act as endocrine disruptors and have the potential to impact the signal pathway and genetic expression in breast cancer cells (Bratton et al., 2012; Tilghman et al., 2012). In addition, the exposure of other risk factors for BC also has disparities in ethnicities. In the comparison between Asian and White females, BC risk factors including menopausal status, age at menarche, age of having first birth, nulliparous status, family BC history, BMI, oral contraceptive use, education level, drinking and smoking status, all had differences (de Bruin et al., 2011; Jernstrom et al., 2001; Setiawan et al., 2006; Menes et al., 2007), and the concentration of estradiol and bioavailable estradiol was higher in Asian women than the US Whites (Setiawan et al., 2006). These variations in genetics and risk factors between races were possible to introduce the racial difference of BC in populations.

One of potential limitations in the study was only one tertiary hospital selected from particular area, which might undermine the representativeness. Tertiary hospitals have standardized procedure in BC diagnosis, especially in the pathological exams, and the test results are generally accepted. The hospital-based case selection was likely to

recruit young patients, not the elderly. The study referred to the population-based cases from National Central Cancer Registry for adjustment and presented an 8-year interval. Age standardization diminished the difference in population structure between China, US and EU and showed supportive result.

In conclusion: taking into account of population structure and racial difference, median age of BC is around 50 years old, nearly 10 years earlier than US and EU. Besides of disparate population structure, genetic background and life style also contributed to the inequities. Although screening program has not been conducted nationwide in China, Chinese women need the screening program at an earlier age. The background mechanisms for the disparities are warranted in further studies.

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