Peer Review File

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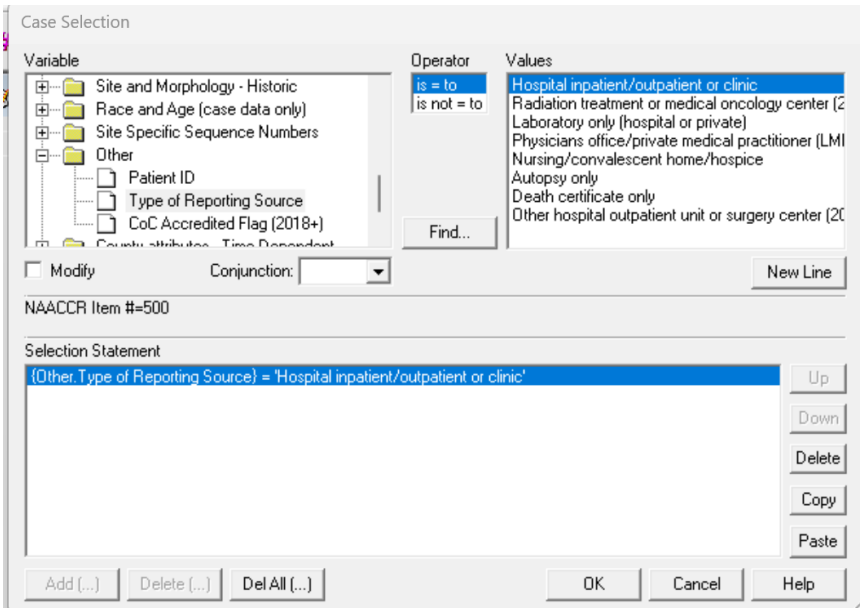
Reviewer Comments:

This study utilized the data from a single hospital (Cancer Hospital, Chinese Academy of Medical Sciences, CHCAMS) in Beijing, China, to examine the clinicopathologic features of 18,768 breast cancer patients in 1999-2014 and compared these cases with those from the Surveillance, Epidemiology, and End Results (SEER) database in the United States during 1999-2014. The findings on quite different clinical and pathological characteristics from a large number of breast cancer cases in this study should be of interest to researchers in China and around the world. However, there are a few issues on the clarities in their descriptions of the two datasets and in their methodological approaches and analyses, which, if addressed well, should improve the quality of the study.

Comment 1. From the beginning and in the methods, this study should have made it clearer that breast cancer patients in 1999-2014 in China were from a single Cancer Hospital in Beijing, whereas breast cancer cases in SEER in the United States were from the population-based cancer registries (18 SEER areas) which included many cases from outpatient clinics or communities (non-hospitalized cases). Patients in Cancer Hospital in Beijing came from many different areas or provinces and could be 'higher stage' cancer cases. Hence, different characteristics between China and SEER would be expected. A better comparison would be to reanalyze the cases who were identified from hospitalized patients only in the SEER database (which included a variable on sources of reporting or where the cases were identified).

Reply 1：Many thanks for your insightful comment. We strongly agree with your suggestion. SEER database includes the type of reporting sources, however, the hospital inpatient mixed up with outpatient or clinic patients. Hence, we discuss this limitation in the article.



Changes in the text: 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 inpatient, outpatient or communities. This may lead to bias and relatively a little higher stage cancer cases in China. (Line 299-304 on Page 11 of tracked version)

Comment 2. Because clinicopathologic features of breast cancer may differ between Chinese or Asians and Caucasians or African populations, it would be helpful to compare breast cancer cases from Cancer Hospital in Beijing with those breast cancer cases from SEER in the USA who were Asian or Chinese. The race and ethnicity variables are available in SEER, making this possible for better comparisons.

Reply 2：Many thanks for your kind suggestion. We strongly agree with your suggestion. We compared the breast cancer cases from Cancer Hospital in Beijing with those breast cancer cases from SEER in the USA who were Chinese, and added the results into the supplementary materials.

Changes in the text: 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 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 in China (30.72% vs 2.14%), but fewer than 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 in China, but were the same with the US (50.15% vs 48.84%). (supplementary materials)

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

	China [N (%)]	The Chinese population in the United States [N (%)]	The United States [N (%)]	χ2	p value
Total	18,685 (100%)	9,417 (100%)	757,357 (100%)		
Age at Diagnosis*				13,119.95	<0.001
<35	1,214 (6.56)	235 (2.50)	14,931 (1.97)		
35-44	4,912 (26.56)	1,397 (14.83)	76,338 (10.01)		
45-54	6,586 (35.62)	2,753 (29.23)	167,286 (21.93)		
55-64	3,915 (21.17)	2,139 (22.71)	186,892 (24.50)		
65-74	1,470 (7.85)	1,571 (16.68)	161,051 (21.11)		
≥75	395 (2.14)	1,322 (14.04)	150,859 (19.77)		
Pathological type				1,768.06	<0.001

Invasive ductal	16,966 (90.8)	7,450 (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)	3840 (40.78)	299,552 (39.55)		
No	15,728 (84.17)	5577 (59.22)	457,805 (60.45)		
Radiotherapy				11,825.18	<0.001
Yes	837 (4.48)	4244 (45.07)	336,100 (44.38)		
No	17,848 (95.52)	5173 (54.93)	421,257 (55.62)		
location				9,859.64	<0.001
Upper	9,674 (51.85)	4,199 (44.59)	334,709 (44.49)		
Central	3,741 (20.05)	504 (5.35)	39,574 (5.26)		
Lower	2,474 (13.26)	1,145 (12.16)	93,550 (12.43)		
others	2,796 (14.99)	3,569 (37.9)	284,516 (37.82)		

*Some information was unknown.

Comment 3. This study should also discuss if and how cancer screening or early detection affected the clinicopathologic features of breast cancer cases in Cancer Hospital in Beijing, or those cases were all identified from diagnostic detection, or some were identified from routine screening. If possible, analysis should incorporate this information.

Reply 3: Many thanks for your insightful comment. We strongly agree with your suggestion. The vast majority of breast cancer cases were identified from diagnostic detection in Cancer Hospital in Beijing due to the routine screening were rare during 1999-2014. We added discuss how cancer screening or early detection affected the clinicopathologic features of breast cancer cases.

Changes in the text: 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). (Line 255-259 on Page 9 of tracked version)

References

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21. Tesfaw A, Demis S, Munye T, et al. Patient Delay and Contributing Factors Among Breast Cancer Patients at Two Cancer Referral Centres in Ethiopia: A Cross-Sectional Study. J Multidiscip Healthc. 2020;13:1391-401. 10.2147/JMDH.S275157.

22. Huang Y, Tong Z, Chen K, et al. Interpretation of breast cancer screening guideline for Chinese women. Cancer Biol Med. 2019;16:825-35. 10.20892/j.issn.2095-3941.2019.0322.

Comment 4. If the study can add some analyses on the patient's outcomes such as survival or mortality and their treatment received (definitive surgeries and chemotherapy) between China and USA, if possible and data are available, it would be helpful and more interesting.

Reply 4：Many thanks for your insightful comment. We strongly agree with your suggestion and added the data of treatment of breast cancer patients in China and USA. Owing to the cross-sectional nature of the study design, the survival and mortality data of China was difficult to obtain. We added the treatment data between China and USA.

Changes in the text: 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 radiotherapy and chemotherapy decreased sharply with the increasing of age both in China and the US (Figure 8a, 8b). (Line 224-228 on Page 8 of tracked version)

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

	China [N (%)]	The United States [N (%)]	χ^2	*p* value
Total	18,685 (100%)	757,357 (100%)		
Age at Diagnosis*			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 (90.8)	622,843 (82.24)		
Invasive lobular	488 (2.61)	75,807 (10.01)		

Invasive	364 (1.95)			
mucinous		19,474 (2.57)		
Invasive	183 (0.98)			
medullary		3,607 (0.48)		
others	684 (3.66)	35,626 (4.7)		
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			11816.12	<0.001
Yes	837 (4.48)	336,100 (44.38)		
No	17,848 (95.52)	421,257 (55.62)		
location			9,853.28	<0.001
Upper	9,674 (51.85)	334,709 (44.49)		
Central	3,741 (20.05)	39,574 (5.26)		
Lower	2,474 (13.26)	93,550 (12.43)		
others	2,796 (14.99)	284,516 (37.82)		

*Some information was unknown.

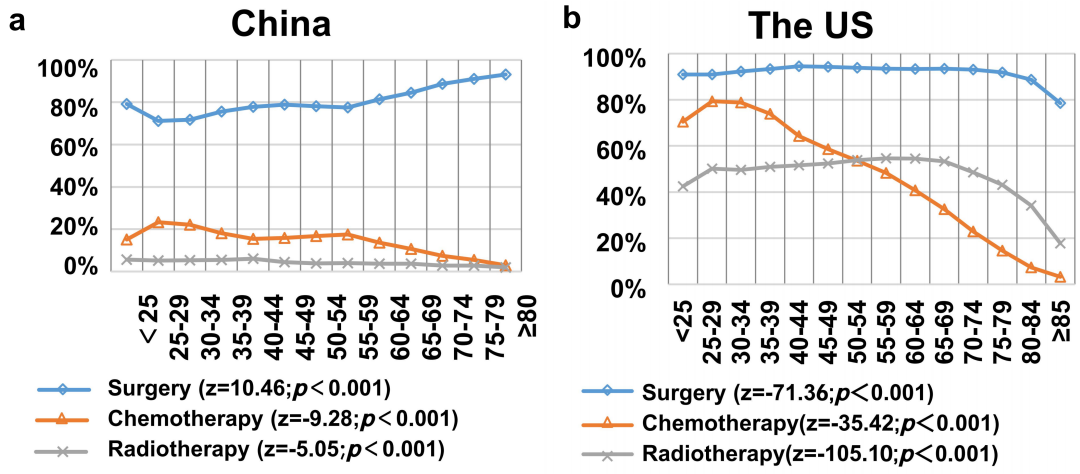

Figure 8a. The treatment changes with age of female breast cancer in China; b. The treatment changes with age of female breast cancer in the United States.