Int J Clin Exp Med 2014;7(4):1116-1121
www.ijcem.com /ISSN:1940-5901/IJCEM1402028

Original Article

Breast cancer molecular subtypes of Uygur and Han in Xinjiang of China

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Received February 9, 2014; Accepted April 15, 2014; Epub April 15, 2014; Published April 30, 2014

Abstract: Purpose: To compare the difference between Uygur and Han patients with breast cancer in molecular subtype. Methods: 4 immunohistochemical (IHC) markers (ER, PR, HER-2 and KI-67) were used to divide Uygur and Han breast cancer patients into 4 subtypes (Luminal A, Luminal B, HER-2 over expression and Basal-like), respectively. statistical analysis were used to evaluate difference in molecular subtype characteristics by race, tumor size, age of onset, menstruation and birth status, histological grade and lymph node metastasis. Results: There is no statistical difference on the molecular subtypes between Han and Uygur. But some characteristics about four subtypes between Han and Uygur have statistical difference like age onset of the Her-2 overexpression cases, subtypes of age less than 35 years, menarche age of the Basal-like cases and tumor size of the Luminal A cases. Between Han and Uygur there is statistical difference on the menarche age, number of childbirths, and tumor size. The HER-2 overexpression and Basal-like subtypes were more likely to be grade III tumors both of Han and Uygur. Between 4 molecular subtypes of Han there have statistical difference in number of metastasis lymph nodes. Conclusions: Our result shows that there are some significant differences between Uygur and Han in the pathological features as well as molecular subtypes. Correct understanding the difference of breast cancer between Uygur and Han can provide guidance for clinical practice.

Keywords: Breast, molecular, subtypes, race

Introduction

Breast cancer remains the most common cancer in the women, regardless of age or race/ethnicity [1, 2]. It's a serious disease which threatens to women's health. Biological target therapy is the most reliable method in the treatment of tumor. Breast cancer is a heterogeneous disease whose component includes many molecular subtypes [3]. We have different target therapy with different subtypes. So the correct characterization for different molecular subtype was the foundation of the personalized treatment. In the 12th St Gallen International Breast Cancer conference, the experts reached a consensus on breast cancer's molecular subtype [4]. Compared to the previous typing method, the consensus on the biggest change is the inclusion of IHC indicators KI-67. The previous typing method is that Luminal A (ER+/PR+, HER-2-), Luminal B (ER+/PR+, HER-2+), HER-2 overexpression (ER-, PR-, HER-2+), and Basal-like (ER-, PR-, HER-2-). In the new typing method is Luminal A (ER+/PR+, HER-2-, KI-67<14%), Luminal B (ER+/PR+, HER-2-, KI-67≥14%; ER+/PR+, HER-2+), HER-2 overexpression (ER-, PR-, HER-2+), Basal-like (ER-, PR-, HER-2-). Therefore, we used the new typing standard to classify the molecular subtype of Uygur and Han patients with breast cancer, and the difference between which was also compared and analyzed.

Materials and methods

Study population

Cases used in these studies were collected in our department in the First Affiliated Hospital of Xinjiang Medical University. All of the cases are invasive breast cancer after surgical resection and pathological diagnosis. Of total 160 cases, Uyghur were 80, Han were 80. The clinical information of all of the cases is available other than survival. All pathological specimens were 10%

Table 1. General pathological features of Uygur and Han

	Han	Uygur	χ^2	*P*-value
Age of onset				
≤35	8 (10%)	12 (15%)	1.809	0.405
36~60	57 (71.25%)	58 (72.5%)		
>60	15 (18.75%)	10 (12.5%)		
Menarche age				
≤12	29 (36.25%)	16 (20%)	6.256	0.044
13~15	28 (35%)	29 (36.25%)		
>15	23 (28.75%)	35 (43.75%)		
Number of childbirths				
0	4 (5%)	4 (5%)	7.483	0.024
≤2	58 (72.5%)	42 (52.5%)		
>2	18 (22.5%)	34 (42.5%)		
Menopausal status				
Premenopausal	45 (56.25%)	38 (47.5%)	1.227	0.268
Postmenopausal	35 (43.75%)	42 (52.5%)		
Tumor grade				
I	8 (10%)	7 (8.75%)	5.264	0.072
II	48 (60%)	35 (43.75%)		
III	24 (30%)	38 (47.5%)		
Tumor size (cm)				
≤2 cm	38 (47.5%)	18 (22.5%)	14.038	0.001
3~5 cm	35 (43.75%)	42 (52.5%)		
>5 cm	7 (8.75%)	20 (25%)		
Number of metastasis lymph nodes				
0	34 (42.5%)	24 (30%)	6.052	0.109
1~4	23 (28.75%)	20 (25%)		
5~10	15 (18.75%)	18 (22.5%)		
>10	8 (10%)	18 (22.5%)		

Chi-square test was used in **Table 1** with SPSS version 11.0.

formalin-fixed, paraffin-embedded, 4 um thickness sections and HE staining. And then the pathological sections were further diagnosed by two senior pathology doctors. Our study was ethically approved by the local ethical committee.

Methods

All of the cases were immunohistochemically stained by 4 IHC markers (ER, PR, HER-2, KI-67). IHC subtypes were assigned as follows: Luminal A (ER+/PR+, HER-2-, KI-67<14%), Luminal B (ER+/PR+, HER-2-, KI-67≥14%; ER+/PR+, HER-2+), HER-2 overexpression (ER-, PR-, HER-2+), Basal-like (ER-, PR-, HER-2-). ER and PR was determined as positive when 1% nuclear staining was evidenced, according to ASCO/CAP guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer [5]. HER-2 was determined as positive if the immunohistochemistry (IHC) result showed 3+. And the case of 2+ should be confirmed by FISH tests, according to ASCO/CAP guideline recommendations for human epidermal growth factor receptor 2 in breast cancer [6]. According to the formation of glandular structure, atypical of nucleus and mitosis, 160 cases were assessed for grade I, II and III [7]. Statistical analyses were used to determine whether the race and molecular subtype associations with tumor size, age of onset, menstruation and birth status, histological grade and lymph node metastasis. Chi-square test (χ^2) was used for the unidirectional ordered R × C contingency table data which the grouping variables are ordered and indicator variables are unordered. *P*-value <0.05 was considered statistical significant. All statistical analyses were performed by SPSS version 11.0.

Result

General pathological features of Uygur and Han

The age of onset was mostly range from 36 to 60. The average age of Han and Uygur was 50.48 years and 48.01 years, respectively. There is no statistically significant difference on the age of onset between Han and Uygur (χ^2=1.809, *P*=0.405). But there is statistical difference on the menarche age (χ^2=6.256, *P*=0.044), number of childbirths (χ^2=7.483, *P*=0.024), and tumor size (χ^2=14.038, *P*=0.001) between Han and Uygur. Compared with Han patients, the Uygur patients had the following characteristics: most patients' menarche age older than 15, number of childbirths more than 2 and the patients' tumor size larger than 5 cm. No statistically significant difference was observed after analysis for menopausal status (χ^2=1.227, *P*=0.268), tumor grade (χ^2=5.264, *P*=0.072) and number of metastasis lymph nodes (χ^2=6.052, *P*=0.109). The above characteristics were summarized in **Table 1**.

Table 2. Molecular subtypes of Han and Uygur

	Luminal A	Luminal B	HER-2+	Basal-like	χ^2	*P*-value
Han	30 (37.5%)	25 (31.25%)	13 (16.25%)	12 (15%)	3.208	0.361
Uygur	27 (33.75%)	20 (25%)	12 (15%)	21 (26.25%)		
Total	57 (35.63%)	45 (28.13%)	25 (15.63%)	33 (20.63%)		

Chi-square test was used in **Table 2** with SPSS version 11.0.

Table 3. The characteristics had statistical difference in different subtypes of Uygur and Han

	Han	Uygur	χ^2	*P*-value
Age onset of the her-2+ cases				
≤35	0	4	5.758	0.029
36~60	11	8		
>60	2	0		
Subtypes of age less than 35 years				
Luminal A	3	2	8.229	0.036
Luminal B	5	2		
HER-2+	0	4		
Basal-like	0	4		
Menarche age of the Basal-like cases				
≤12	9	3	11.740	0.003
13~15	2	8		
>15	1	10		
Tumor size of the Luminal A cases				
≤2	17	6	7.600	0.019
3~5	12	17		
>5	1	4		

Chi-square test was used in **Table 3** with SPSS version 11.0.

Different molecular subtype characteristics of Uygur and Han

Most tumors' molecular subtypes of Han and Uygur were Luminal A. Distribution of molecular subtypes was summarized in **Table 2**. There is no statistical difference on the molecular subtypes between Han and Uygur (χ^2=3.208, *P*=0.361). Other characteristics about four subtypes have statistical difference between Han and Uygur were in the **Table 3**. Uygur patients tend to had a younger age in subtype HER-2 overexpression (χ^2=5.758, *P*=0.029), higher proportions of non-Luminal subtype in age of onset less than 35 (χ^2=8.229, *P*=0.036), higher proportions of older age of menarche in subtype Basal-like (χ^2=11.740, *P*=0.003), and had larger tumor size in Luminal A (χ^2=7.600, *P*=0.019). Molecular subtypes of Han have statistical difference in tumor grade (χ^2=15.280, *P*=0.009) and number of metastasis lymph nodes (χ^2=17.657, *P*=0.022) (**Table 4**). Molecular subtypes of Uygur also have statistical difference in tumor grade (χ^2=13.084, *P*=0.025) (**Table 5**).

Discussion

The concept of tumor molecular subtype was first proposed by United States' National Cancer Institute in 1999. Its purpose is to establish a new classification method by tumor's molecular characteristics. Reflect tumor's biology characteristics and to better guide the clinical. In 2000, Perou studied the breast cancer's gene expression profile and first proposed the molecular subtypes of breast cancer [8]. The gene expression study is more complex, and is not suitable for clinical testing. So experts proposed approximate molecular typing of breast cancer by immunohistochemistry indicators. In the 12th St Gallen International Breast Cancer Conference experts proposed a new approach to the classification of molecular subtypes of breast cancer.

In the present study, molecular subtypes luminal A, luminal B, HER-2 overexpression and Basal-like were distributed as 37.5%, 31% 25, 16.25% and 15% for Han, and 33.75%, 25%, 15% and 26.25% for Uyghur. In a study from USA [9], the subtypes luminal A, luminal B, HER-2 overexpression and Basal-like were distributed as 64%, 11%, 5% and 11% for whites, and 48%, 8%, 7%, and 22% for African Americans, respectively. Our results is different with their conclusions in subtypes luminal A, and luminal B, the possible reason may be that our subtype method with the IHC indicators KI-67 being added. Meanwhile, it can be seen that compared to Americans more HER-2 overexpression was seen in Asians, which is similar to a report from Thailand [10]. And another study from the California Cancer Registry reported that Asian women had a significantly

Table 4. Tumor grade and Number of metastasis lymph nodes of different subtypes of Han

	Luminal A	Luminal B	HER-2+	Basal-like	χ^2	*P*-value
Tumor grade						
I	4	8	0	1	15.280	0.009
II	22	48	5	4		
III	4	24	8	7		
Number of metastasis lymph nodes						
0	15	10	2	7	17.657	0.022
1~4	9	10	3	1		
5~10	6	2	4	3		
>10	0	3	4	1		

Chi-square test was used in **Table 4** with SPSS version 11.0.

Table 5. Tumor grade of different subtypes of Uygur

	Luminal A	Luminal B	HER-2+	Basal-like	χ^2	*P*-value
Tumor grade						
Grade 1	6	1	0	0	13.084	0.025
Grade 2	14	10	4	7		
Grade 3	7	9	8	14		

Chi-square test was used in **Table 5** with SPSS version 11.0.

increased risk of being diagnosed with HER2-positive breast cancer subtypes [11]. So, there may be the difference existed in breast cancer between Asian and American women.

The age of onset between Asian and Western women with breast cancer have differences. Leong reported that the peak onset age of the breast cancer ranged from 40 to 50 years for Asian women and 60 to 70 years for Western women [12]. Our results show that the peak onset age of the breast cancer ranged from 35 to 60 years for both of Uygur and Han women, and the average age of Han and Uygur was 50.48 years and 48.01 years, respectively. Our results are consistent with Leong's reported. Furthermore, our study find that the age of onset in subtype HER-2 overexpression and molecular subtypes between age of onset less than 35 of Han and Uygur have significantly differences. This difference has not been reported in the previous. Young age of onset correlates with worse prognosis in breast cancer [13]. In our study the Uygur and Han women's age of onset are younger than western women. This prompted the Asian women with breast cancer maybe have poor prognoses.

The incidence and the prognosis of breast cancer are related with menarche, delivery and menopause [14, 15]. In our study, the age of menarche in subtypes Basal-like of Uygur and Han and the menopausal status in Luminal B of Han and Uygur have significantly differences. It explains breast cancer's occurrence related with race and some molecular subtypes.

Tumor grade, tumor size and number of metastasis lymph nodes is different between African-American and white breast cancer patients [16-18]. Compared with white breast cancer patients, African-American patients have the larger tumor, higher tumor grade and more metastasis lymph nodes. These characteristics are connected with the poor prognosis. Tumor size between Han and Uygur had statistical difference, Uygur patients have lager tumor. The tumor grade in 4 subtypes both of Han and Uygur had statistical difference, the HER-2 overexpression and Basal-like subtypes were more likely to be grade III tumors, it can be concluded that the HER-2 overexpression and Basal-like subtypes have high tumor grade. The result is similar to Chuthapisith's [10]. Studies have demonstrated Luminal A have a good survival rate and prognosis [19, 20]. Compared with Han patients, Uygur patients have lager tumor in Luminal A. It also explained the Uygur patients have a poor prognosis.

However, there are some limitations in this study. Firstly, the molecular subtype is based on the gene microarray. The immunohistochemical subtype is an approximate molecular subtype; it may not be accurately to subtypes. Secondly, there is no uniform testing standards of the marker Ki-67, and the identifying standard of Ki-67 is 14%, how to determine 14% is varies with different doctors.

In conclusion, Uygur patients had some poor prognosis features, and there are some differences between Uygur and Han breast cancer patients in pathological features and molecular subtypes. The different nationalities molecular

subtype does have some differences, it is undoubtedly a fact. So correct understanding the differences of breast cancer between different nationalities is very necessary.

Acknowledgements

This study was supported by the Xinjiang Uygur Autonomous Region, Science and Technology Supporting Project (NO201291172).

Disclosure of conflict of interest

There were no conflicts of interest in the present study.

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