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Breast Cancer Subtypes in Asian-Americans Differ According to Asian Ethnic Group

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Abstract

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Breast cancer prognosis and breast cancer molecular subtype vary by race/ethnicity. We determined whether the distribution of breast cancer subtypes varies among different Asian ethnic groups. Using immunohistochemical surrogates for the four molecularly defined breast cancer subtypes, we characterized breast cancer subtype for 346 Asian subjects treated at two New York City institutions. We found that Chinese and Japanese had a higher proportion of good-prognosis luminal A cancers (66.7 and 80.0%, respectively) compared to Filipinos and Koreans (48.5 and 47.1%) ($P = 0.001$). Filipinos had a higher proportion of HER-2/neu positive cancers (45.6%) compared to other ethnic groups (23.6%) ($P = 0.002$). Koreans had a higher proportion of triple negative cancers (23.5%) compared to other ethnic groups (7.5%) ($P = 0.06$). The results suggest that differences exist in breast cancer tumor biology among distinct Asian ethnic groups and have implications for cancer care and research. Future studies of breast cancer in Asian-Americans should distinguish among the different ethnic groups.

Keywords

Asian ethnicity; Breast cancer; Her2/neu; Breast cancer subtypes

BACKGROUND

In the year 2007, over 200,000 women were diagnosed with breast cancer in the United States. Of these cases, over 6,000 were in women of Asian descent. Breast cancer incidence and breast cancer mortality varies by race and ethnicity [1, 2]. The breast cancer incidence rate is highest in non-Hispanic white women, followed by African-Americans, Asian-Americans/Pacific islanders, and Hispanics/Latinas. In contrast, breast cancer mortality is highest for African-Americans and lowest for Asian-Americans. Although Asian-American women have a lower overall breast cancer mortality rate compared with other races, this more favorable prognosis may not be equally distributed among all Asian ethnic groups. Indeed, in studies in which breast cancer mortality has been compared between individual Asian ethnic groups, significant differences have been found. In one study of breast cancer in a San Francisco Bay area population, Chinese and Japanese women were found to have an equal (Chinese) or better (Japanese) survival compared with Caucasian women. Filipino women had a lower survival rate [3]. In a study of breast cancer in Hawaiian residents, Filipino women were more likely, and Japanese women less likely, to die of breast cancer compared with Caucasian and Chinese women [4]. Finally, among patients included in a Northern California Cancer Registry, Filipino women were found to have the highest breast cancer mortality rate among all Asian ethnic groups [5].

The worse prognosis of Filipino women may be related to lifestyle or to environmental factors that may impact on breast cancer prognosis. Alternatively, genetic influences could contribute. Recently, breast cancer molecular subtype has emerged as an important determinant of breast cancer prognosis. The luminal A subtype, which includes breast cancers that overexpress ER and PR but not Her2/neu, is associated with a favorable prognosis, whereas the basal subtype, which includes ER, PR, and Her2/neu negative breast cancers, is associated with the worst prognosis. The luminal B and Her2/neu-like subtypes, which exhibit Her2/neu activation gene signatures, are associated with an aggressive natural

history and high recurrence rates [6] and are intermediate in prognosis between luminal A and basal subtypes.

The expression of ER, PR, and Her2/neu on breast cancers from Asian-Americans has not been well-characterized. In an analysis of ER and PR by race and ethnicity among participants of the Women's Health Initiative (WHI), it was reported that expression of ER and PR did not differ between Asians and Caucasians; however, that study was limited by the small number of Asians who participated in the WHI [7]. In contrast, using data from the NCI SEER registries, which include registries from Hawaii and California, two states having a large Asian minority population, a 1.4 fold increase in ER negative and PR negative cancers in Asians compared with non-Hispanic whites was found [8]. Assigning molecular subtypes, which incorporate Her2/neu status, in these studies is limited as Her2/neu testing only became standard in the late 1990s.

In order to explore the mechanisms contributing to differences in breast cancer outcomes seen among women of Asian ancestry, we investigated whether the prevalence of breast cancer molecular subtypes varied among women of different Asian ethnic groups.

METHODS

Medical and pathology records were reviewed retrospectively. Asian women with invasive breast cancer were identified using outpatient registration records and cancer registries from two New York City institutions, Weill Cornell Medical Center of New York Presbyterian Hospital and the Beth Israel Medical Center. Asian ethnicity was assessed using self identified ethnicity as recorded in the medical records, or by birthplace together with surname and/or parent's first names as recorded in the registration record. Patients of Chinese, Filipino, Japanese or Korean ethnicity who were diagnosed with stage I, II, or III invasive breast cancer between 1997 and 2007 were identified. Patient data for age, number of positive lymph nodes, tumor size, stage, grade, ER, PR, and HER-2/neu at diagnosis were recorded. Breast cancer molecular subtype was assigned using immunohistochemical surrogates according to published definitions [9, 10]. Information for grade, stage, ER, Her2/neu, and breast cancer subtype was available for 90, 96, 98, 90, and 90%, respectively, of subjects. Definitions of ER, PR, and Her2/neu positivity were made according to the institution's pathology standards. Stage was determined according to the AJCC Cancer Staging Manual, 6th edition [11]. This study was approved by the Institutional Review Boards of Weill Cornell Medical College and Beth Israel Medical Center.

Descriptive statistics (including mean, standard deviation, frequency, percent), stratified by the four molecularly defined breast cancer subtypes, were calculated for demographic, clinical, and immunohistochemical factors of interest. The Chi-square test or Fisher's exact test was used, as appropriate, to compare the prevalence of clinical and immunohistochemical characteristics between the four molecularly defined breast cancer subtypes. The ANOVA test was used to compare mean age between the four molecularly defined breast cancer subtypes. All P-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SPSS Version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

We identified 346 patients of Asian ethnicity diagnosed with nonmetastatic invasive breast cancer between 1997 and 2007. There were 209 (59.9%) Chinese, 77 (22.1%) Filipino, 38 (10.9%) Japanese, and 22 (6.3%) Korean subjects included in the analysis. Table 1 shows the mean age of subjects and the characteristics of invasive breast cancer by ethnicity. The mean age of Koreans with breast cancer was 39.2 ± 10.8 years, which was younger than the mean age of Chinese (51 years), Filipino (51 years), and Japanese (47 years) women ($P < 0.0001$ by ANOVA test). Japanese had a lower proportion of stage III disease (8%) compared to the other ethnic groups. ($P = 0.02$ by Chi-square test). Filipino and Korean women had a higher proportion of Grade III tumors (53.5 and 63.2%, respectively) compared to Chinese and Japanese women (33.5 and 27.8%, respectively) ($P = 0.01$ by Chi-square test). Filipino and Korean women had a lower proportion of ER positive cancers (68.0 and 52.4%, respectively) compared to Chinese and Japanese women (82.1 and 86.5%, respectively) ($P = 0.001$ by Chi-square test). Filipino women had a higher proportion of HER-2/neu positive cancers (45.6%) compared with the other ethnic groups (23.6%) ($P = 0.002$ by Chi-square test).

The distribution of breast cancer subtypes by ethnicity is shown in Table 2. Overall, 63.1% of breast cancers were classified as Luminal A (ER-positive and/or PR-positive, Her2/neu-negative), 16.5% as Luminal B (ER-positive and/or PR-positive, Her2/neu- positive), 12.0% as Her2/neu-like (ER- and PR-negative, Her2/neu-positive), and 8.4% as basal-like (triple negative). Breast cancer subtype differed significantly by ethnicity ($P = 0.004$ by Chi-square test). Chinese and Japanese women had a higher proportion of luminal A cancers (66.7 and 80.0%, respectively) and a lower proportion Her2/neu-like cancers (9.0 and 2.9%, respectively) compared with Filipinos and Koreans ($P = 0.001$). Conversely Filipinos and Koreans had a higher proportion of Her2/neu-like cancers (25 and 18%, respectively) compared to Chinese and Japanese (10 and 3%, respectively). Filipino women tended to have a higher proportion of luminal B tumors (22.1%) compared to the other ethnic groups (14.9%) ($P = 0.22$). Korean women had a higher proportion of triple negative cancers (23.5%) compared to all other ethnic groups (7.5%) ($P = 0.06$ by Fisher's exact test).

Discussion

Gene expression profile assays have identified breast cancer molecular subtypes that confer distinct breast cancer prognoses. Our retrospective analysis shows that the distribution of breast cancer subtypes among Asian women of Chinese, Filipino, Japanese and Korean descent varies by Asian ethnicity. Remarkably, the incidence of Her2/neu positive breast cancers in Filipino women was 46%, which was higher than for all other Asian ethnic groups. Filipino women had an increase in both the luminal B type as well as the Her2/neu-like cancers. It was recently reported that Asian-Americans in California have a 1.26–2.0 fold increase in numbers of Her2/neu positive breast cancers compared with Caucasian women [12, 13]. The study from Telli et al. [13] was a population based study using data from the California Cancer Registry. Although the results of our study cannot be compared directly to that study, due to differences in statistical methods and to definitions of molecular subtypes, it is nonetheless interesting to note that the absolute proportion of Her2/neu

positive cancers in Japanese (19%) and Chinese (26%) reported by Telli is similar to what we have reported (14 and 25%, respectively). The proportion of Filipinos and Koreans with Her2/neu positive cancer in that study was 31 and 36%, respectively. Thus the results from our New York institutional study share a similar trend with the results from the population-based California study, with Filipino and Koreans having increased proportion of Her2/neu positive cancers compared with Chinese and Japanese. It is interesting to hypothesize that the differences in the absolute numerical values in our studies may be attributable to differences in the characteristics of the immigrant populations of California versus New York, such as the number of generations in the US. Alternatively, methods of Her2/neu testing and reporting are known to be highly dependent upon pathology laboratory technique, and more variability in results would be expected in a population based study involving multiple institutions, compared with our study, in which only two institutions were involved.

Although our analysis included only a small number of Korean-American women, we found that Korean women had a statistically significant increase in triple negative cancers compared with the other Asian groups. Korean women in our series were more likely to be younger in age. The younger age at breast cancer diagnosis in Korean-American women in our study is consistent with the younger age at breast cancer diagnosis in Korea, where the peak incidence occurs between the ages of 45 and 50 [14]. This is earlier than the peak incidence at diagnosis in the United States, which occurs between ages 55 and 64 [15]. Younger age may partially account for the higher incidence of ER negative cancers in our Korean subjects, as younger women are more likely to present with ER negative cancers. In addition, young Korean women with breast cancer were reported to have a high prevalence of BRCA 1 and 2 mutations, which were more often associated with ER negative cancers [16].

Estrogen positive breast cancers have been shown to be associated with early age at menarche, nulliparity, high body mass index (BMI), and type of body fat distribution [17–19]. Her2/neu-positive breast cancers have not been linked to specific lifestyle or genetic factors. However, a recent finding that postmenopausal women in the Women's Health Initiative who received hormone replacement therapy (HRT) were more likely to develop Her2/neu positive cancers compared with women who did not receive HRT [20] suggests that exogenous estrogen/progestin may be one factor that contributes to the development of Her2/neu positive cancers. Hormone levels have been reported to vary across racial/ethnic groups [21, 22] and it is possible that hormonal differences exist that predispose Filipino women toward developing Her2/neu expressing cancers.

In summary, we have found that differences exist in the distribution of breast cancer subtypes in Asian-American women with breast cancer. The higher incidence of luminal A breast cancers in Japanese and Chinese women may explain their better breast cancer outcomes compared with other Asians that has been previously reported. Conversely, the higher prevalence of Her2/neu positive breast cancers in Filipino women may contribute to their worse prognosis. If so, breast cancer outcomes would be expected to improve for Filipino women in the current era of anti- Her2/neu targeted therapy. Nevertheless the treatment of Her2/neu positive cancers with chemotherapy and Her2/neu targeted agents are

associated with significant toxicity and cost. In contrast, chemotherapy can often be avoided in luminal A cancers, with a program of treatment consisting of hormonal therapy alone sufficient. Our results highlight the need for additional research to investigate the genetic and lifestyle risk factors that predispose Filipino women to develop Her2/neu positive breast cancers. If modifiable risk factors are found, the incidence of these aggressive cancers in this population may be able to be reduced. Our results also emphasize the importance of distinguishing among the different Asian ethnic groups when studies are done that investigate breast cancer and race/ethnicity in Asians, especially if comparisons are being made to the Caucasian population.

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Table 1

Breast cancer characteristics in Asian ethnic groups

Characteristic	Ethnicity				*P*-Value
	Chinese (*N* = 209)[a]	Filipino (*N* = 77)	Japanese (*N* = 38)	Korean (*N* = 22)	
Age, mean ± SD	51.4 ± 13.1	51.6 ± 10.3	47.2 ± 10.9	39.2 ± 10.8	<0.0001*
Stage, *N* (%)					
I	109 (54.5)	34 (45.9)	17 (44.7)	3 (15.0)	0.02
II	64 (32.0)	31 (41.9)	18 (47.4)	14 (70.0)	
III	27 (13.5)	9 (12.2)	3 (7.9)	3 (15.0)	
Grade, *N* (%)					
I	33 (17.8)	9 (12.7)	7 (19.4)	0 (0.0)	0.01
II	90 (48.6)	24 (33.8)	19 (52.8)	7 (36.8)	
III	62 (33.5)	38 (53.5)	10 (27.8)	12 (63.2)	
ER, *N* (%)					
Positive	170 (82.1)	51 (68.0)	32 (86.5)	11 (52.4)	0.001
Negative	37 (17.9)	24 (32.0)	5 (13.5)	10 (47.6)	
PR, *N* (%)					
Positive	139 (68.1)	43 (57.3)	30 (83.3)	11 (52.4)	0.02
Negative	65 (31.9)	32 (42.7)	6 (16.7)	10 (47.6)	
Her2/neu, *N*(%)					
Positive	47 (24.9)	31 (45.6)	5 (13.9)	5 (29.4)	0.002
Negative	142 (75.1)	37 (54.4)	31 (86.1)	12 (70.6)	

*By ANOVA test; all other *P* values calculated by Chi-square test

[a]Number analyzed for each category may not total 209, 77, 38, and 22 due to missing data for some patients

Table 2

Distribution of breast cancer subtypes by Asian ethnic group

Ethnicity	Breast cancer subtype[a]				Total
	Luminal A	Luminal B	Her2/neu	Basal-like	
Chinese, *N* (%)	126 (66.7)	30 (15.9)	17 (9.0)	16 (8.5)	189
Filipino, *N* (%)	33 (48.5)	15 (22.1)	16 (23.5)	4 (5.9)	68
Japanese, *N* (%)	28 (80.0)	4 (11.4)	1 (2.9)	2 (5.7)	35
Korean, *N* (%)	8 (47.1)	2 (11.8)	3 (17.6)	4 (23.5)	17
Total, *N* (%)	195 (63.1)	51 (16.5)	37 (12.0)	26 (8.4)	309

$P = 0.004$ by overall Chi-square test

[a] *Definitions* Luminal A: ER pos and/or PR pos, Her2/neu neg; Luminal B: ER pos and/or PR pos, Her2/neu pos; Her2/neu: ER neg, PR neg, Her2/neu pos; basal-like: ER neg, PR neg, Her2/neu neg