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Original Article

Distinct breast cancer subtypes in women with early-onset disease across races

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Abstract: *Background:* Racial disparities among breast cancer (BCa) patients are known but not well studied in early-onset BCa. We analyzed molecular subtypes in early-onset BCa across five major races. *Methods:* A total of 2120 cases were included from non-Hispanic White (NHW), African American (AA) and Hispanic, Chinese and Indian. Based on ER, PR and HER-2 status, BCa was classified into 4 intrinsic subtypes as Luminal A, Luminal B, HER2/neu overexpression and Triple negative BCa (TNBC) subtypes. Data was stratified according to race and age as younger/early-onset group (40-years and younger) and older group (50-years and older). *Results:* In early-onset BCa, incidence of TNBC was significantly higher ($p = 0.0369$) in Indian women followed by AA, Hispanic, NHW and Chinese women. Incidence of Her2 over-expression subtype also was highest in Indian women, followed by Hispanic, Chinese, AA and NHW women. In contrast, Luminal B subtype was most significantly higher in AA women ($p = 0.0000$) followed by NHW ($p = 0.0002$), Chinese ($p = 0.0003$), Hispanic (0.0128) and Indian ($p = 0.0468$) women. Luminal A subtype was most significantly reduced in Indian women ($p = 0.0113$) followed by Hispanic, AA, NHW and Chinese women. These results were based on statistical analysis with the mean of older group populations. *Conclusions:* These results show significant disparities in receptor subtypes across races. This study will contribute in developing optimal clinical trial protocols and personalized management strategies for early-onset BCa patients.

Keywords: Breast cancer subtypes, races, global, receptor, risk

Introduction

Breast cancer (BCa) is the most common cancer among women worldwide. Racial disparity in BCa has been recognized for years and is considered a key factor affecting incidence and mortality [1]. Molecular subtypes dictate prognosis and treatment strategies, and the interactions of race or ethnicity with age have contributed significantly to the heterogeneity of BCa.

In the U.S. population, BCa incidence rates in age-adjusted populations are higher in Non-Hispanic White (NHW) women than other races [2, 3]. However, among women with early onset BCa and/or women in younger age group (40 years and younger), the incidence rates are higher among African American (AA) women than NHW women and those of other races. In older age group women (50 years and older), BCa rates remain higher among NHW than women of AA and other races, similar to observations in the age-adjusted population [3]. However, mortality rates are consistently higher in AA women of all ages, followed by NHW, Asian/Pacific Islander, Hispanic and Native American women [3]. Researchers have popularly termed this disparity effect as the Black-White crossover [4], mainly attributable to high-

er rates of triple negative BCa (TNBC) in younger AA women and higher rates of Luminal A type BCa in older NHW women [5]. Similarly, other studies [6-11] have reported a higher incidence of TNBC in AA women than women of other races, and it has been more pronounced among younger women. Additionally, larger tumor size, higher grades and higher incidence of medullary tumors and metastasis are found in AA women than in women of other races [12-14]. Largely, these observations have explained the higher mortality rates among AA women and directed attention to racial disparity in early onset BCa. Consequently, AA women in ages 30 to 39 have been identified as a high risk group and are offered routine mammography screening [15].

BCa incidence and mortality rates for Asian/Pacific Islander, Native American and Hispanic women have remained lower than for NHW or AA women [16, 17]. Prior studies conducted on age-adjusted U.S. populations have shown a higher risk for the HER2/neu overexpression subtype [18, 19] and lower risk for the TNBC subtype [10, 19] in Asian women. BCa in native Chinese women has been characterized as involving larger tumors, later stage at diagnosis, lower ER/PR expression and higher HER2/neu expression than BCa in NHW women [20]. Among Asian women, apart from the racial disparity, there may be an additional disparity of nativity in BCa populations that are classified as U.S. born, immigrants or natives of their respective countries. Some of the studies [21, 22] on Asian BCa population have demonstrated variations in the molecular and pathological characteristics among women of different nativity. Interestingly, this disparity of nativity was not apparent when observing risk of TNBC in AA women. Elevated risk was also reported among contemporary populations in continental Africa [23-25] suggesting the presence of a heritable risk factor for TNBC in all of the African ancestry [24, 26]. Researchers have suggested that genetic or other non-environmental contributions may explain the higher incidence of TNBC among AA women [19]. Unlike AA women, most of the Hispanic and NHW women diagnosed with TNBC are younger than 40 years of age [10, 27-29]. Asian women of this age group are least likely to be diagnosed with TNBC subtype as compared to other races [8, 21, 30].

Gene enrichment analysis revealed 367 significant gene sets that specifically distinguished tumors in younger and older women [31], confirming that BCa at a younger age is a unique entity characterized not only by adverse prognostic features [32-38] but also by diverse underlying biology. Recently, U.S. Preventive Services Task Force (USPSTF) [39] challenged the previously recommended age of 40 years to begin BCa screening with annual mammography, which was advocated by the American College of Surgeons, American Cancer Society and the National Comprehensive Cancer Network. In this study, we compared BCa subtypes based on ER, PR and HER2/neu receptor expression in patients with early onset BCa to the older group patients among different races including AA, NHW, Hispanic, Chinese and Indian women. We defined early onset BCa (younger group) as patients with age of 40 years and younger as established by previous studies [7, 8, 12, 40-45].

Materials and methods

Identification of tissue specimens

The surgical pathology databases were queried for invasive breast ductal carcinoma at the participating institutions. All data was de-identified and the study received Institutional review board (IRB) approval from each participating institution. The study used patient race data from Memorial Sloan Kettering Cancer Center for AA patients, New York University School of Medicine for NHW patients, The University of Texas MD Anderson Cancer Center for Hispanic patients, The First Hospital of Jilin University (China) for native Chinese patients and Rajiv Gandhi Cancer Institute & Research Centre (India) for native Indian patients. All of these institutions are specialized or quaternary care centers that receive patients from diverse geographical areas or states. Information on race was reported by patients. Stratification was performed in 2 groups according to patient age at diagnosis. Patients in younger group (the study population) were 40 years of age or younger and those in the older group (the reference population) were 50 years of age or older. Patients in both groups were selected from a defined period in medical records as consecutive cases. However, these defined periods varied across the participating institutions as illustrated in **Table 1**. Clinical and pathological features including age, race, grade, tumor stage and ER, PR, HER2/neu status (both by

Table 1. Number of Cases in each Molecular Subtype, Race and Age Group

	Study Population (Younger Group of ≤ 40 yrs)					Reference Population (Older Group of ≥ 50 yrs)				
	NHW	AA	Hispanic	Indian	Chinese	NHW	AA	Hispanic	Indian	Chinese
Period of Diagnosis	2008-2012	2006-2012	2006-2012	2009-2011	2005-2010	2008-2012	2006-2012	2006-2012	2009-2011	2005-2010
Number of Cases (N)	108	108	281	114	263	198	111	170	507	260
Luminal A	69	60	151	49	173	165	69	115	262	170
Luminal B	15	16	34	13	36	12	9	19	63	14
Her2 Overexpression	6	7	32	16	22	9	8	11	73	33
TNBC	18	25	64	36	32	12	25	25	109	43
Total Her2 Positive	21	23	66	29	58	21	17	30	136	47

Total Her2 Positive = Lum B + Her2 overexpression.

Table 2. Percentage of Cases in each Molecular Subtype, Race and Age Group

	Study Population or Younger Group					Reference Population or Older Group				
	NHW	AA	Hispanic	Indian	Chinese	NHW	AA	Hispanic	Indian	Chinese
Luminal A	63.89%	55.55%	53.73%	43%	65.77%	83.33%	62.16%	67.65%	51.68%	65.40%
Luminal B	13.89%	14.81%	12.10%	11.40%	13.69%	6.06%	8.11%	11.17%	12.42%	5.40%
Her2 Overexpression	5.55%	6.48%	11.40%	14%	8.36%	4.55%	7.20%	6.47%	14.38%	12.70%
TNBC	16.66%	23.15%	22.77%	31.57%	12.20%	6.06%	22.52%	14.70%	21.50%	16.50%
Total Her2 Positive	19.44%	21.29%	23.50%	25.40%	22.05%	10.61%	15.31%	17.64%	26.80%	18.10%

immunohistochemistry and fluorescence in situ hybridization, wherever necessary) were recorded. Grade and stage information was recorded only for the study population. All slides were reviewed by local pathologists and the same diagnostic criteria, grading and classification scheme was used.

Methodology of receptor testing

The data of immunohistochemical (IHC) study on ER, PR, HER2/neu was retrieved from each participating institution, all of which had a similar staining protocol. All markers were assessed on 4-micron thick sections of formalin fixed paraffin embedded tissue. IHC staining for HER2/neu receptor protein was performed by the HercepTest (FDA approved) using a non-biotin polymer system. For purpose of this study and to maintain harmonization among the participants, nuclear stain in 10% or more of tumor cells by IHC to determine ER or PR was considered positive. We also analyzed data with 1% as the cut off as per criteria established by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines [46], which was available for some of the study populations. However, the difference between criteria with 1% and 10% staining was insignificant and did not affect the results. HER2/neu staining results were determined using criteria established by the ASCO/CAP guidelines [47] that defined positive HER2/neu as 3+ immunostaining on the membrane, or 2+ membranes staining with FISH amplification [47] ratio > 2.0.

Classification of molecular subtypes

Traditionally ER and PR were used to classify BCa subtypes. Luminal A and B were typically classified on the basis of ER, PR and Ki67. However, in most of the recent studies [5-7, 10, 45, 48-54] on racial disparity, patients with BCa were classified into 4 intrinsic molecular subtypes as Luminal A (ER+ and/or PR+ and HER2/neu-), Luminal B (ER+ and/or PR+ and HER2/neu+), HER2/neu over-expression (ER-, PR- and HER2/neu+) and Triple negative BCa (ER-, PR- and HER2/neu-). Consistent with the recent studies, we also used these 4 intrinsic subtypes for the molecular classification.

Statistical analysis

Distribution of patient and tumor characteristics such as age and molecular subtype were grouped by race. Frequency distribution comparison was achieved with chi-square and Fisher's exact tests. Multi-group comparison was done with the analysis of variance method. The Z-test was used to compare the study population average with the mean of the reference population.

Results

We have evaluated a total of 2120 patients with BCa across five major races - NHW (US patients), AA (US patients), Hispanics (US patients), Chinese (Jilin, China) and Indian (Delhi, India). The numbers of patients in each age group and race are shown in **Table 1**. Age distribution, tumor grade, staging and nodal status in the younger group (study group) are shown in **Figure 1**.

Age, tumor grade and stage disparities at diagnosis across races for early-onset BCa

Distribution curves of age at diagnosis showed a linear curve across all races, as observed in **Figures 1A**-**5A**. The peak in each of these curves was usually seen at the age of 39 years. We did not find a significant difference among races. It can be suggested that there is no significant racial disparity regarding age at diagnosis among women with early onset BCa.

Histological grade is an important factor in determining the aggressiveness of BCa. In a comparison of younger group women across all races, more aggressive cancers were observed in AA women, with 74% of this population presenting with grade 3 tumors. This was followed by Hispanic (65.8%), Indian (62.2%), NHW (44%) and Chinese women (35.95%). Grade 1 tumor differentiation was most commonly seen in NHW women (11%) and least commonly in AA women (1%). These observations suggest that younger AA, Hispanic and Indian women were more likely to have grade 3 or poorly differentiated cancers, while younger NHW and Chinese women were more likely to have grade 1 and 2 or well-differentiated cancers. Racial disparity was most remarkable when observed between younger AA and Chinese women in terms of histological tumor grade.

Pathological staging is important to assess the extent of disease and determines the best management protocol. We observed that about

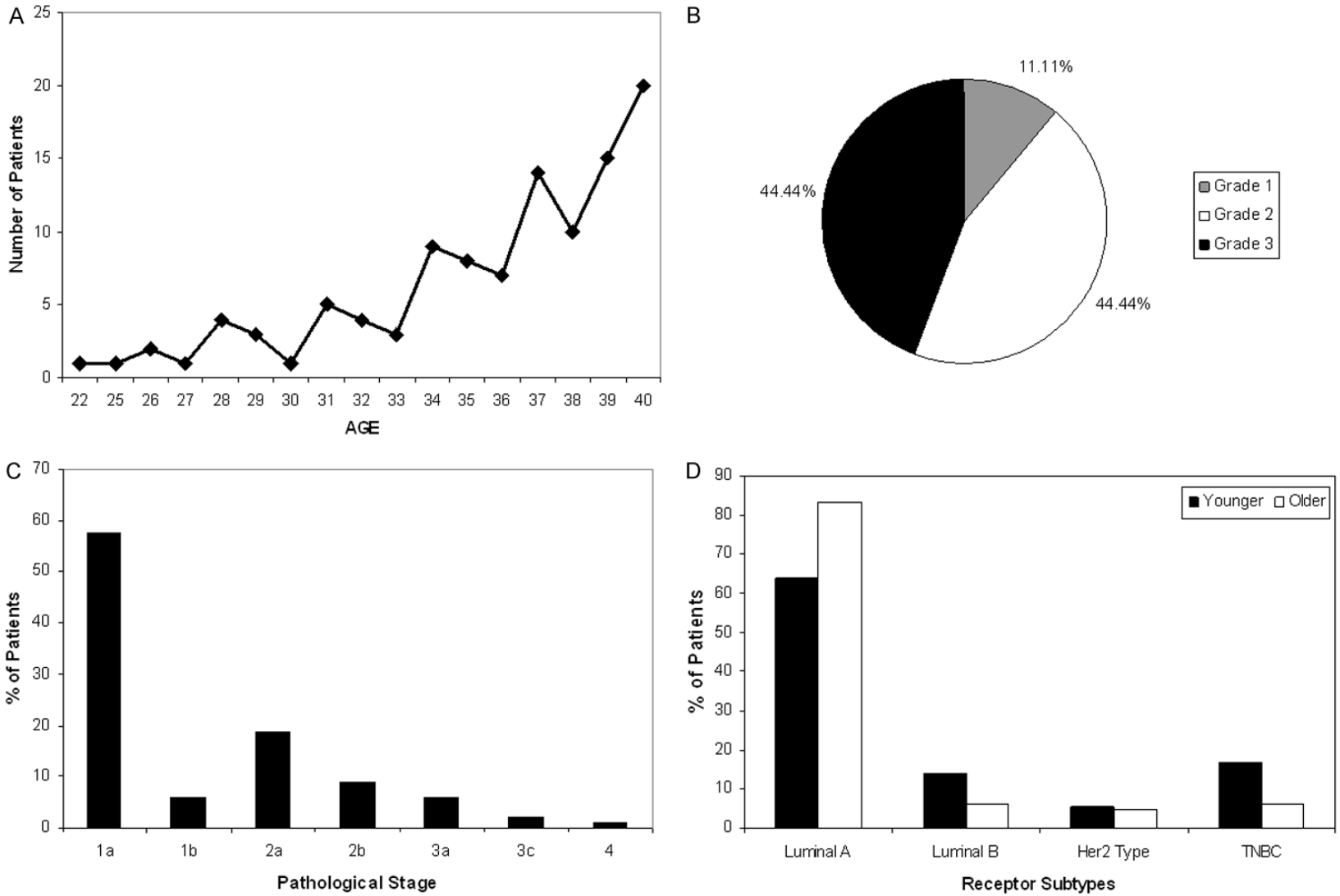

Figure 1. Clinical and pathological characters of early onset breast cancer in non-hispanic white patients. A. Age distribution curve of the NHW younger group. B. Distribution in NHW younger group by Histological grade. C. Distribution in NHW younger group by Pathological stage. D. Percentage of women in NHW younger and older groups for each receptor subtype.

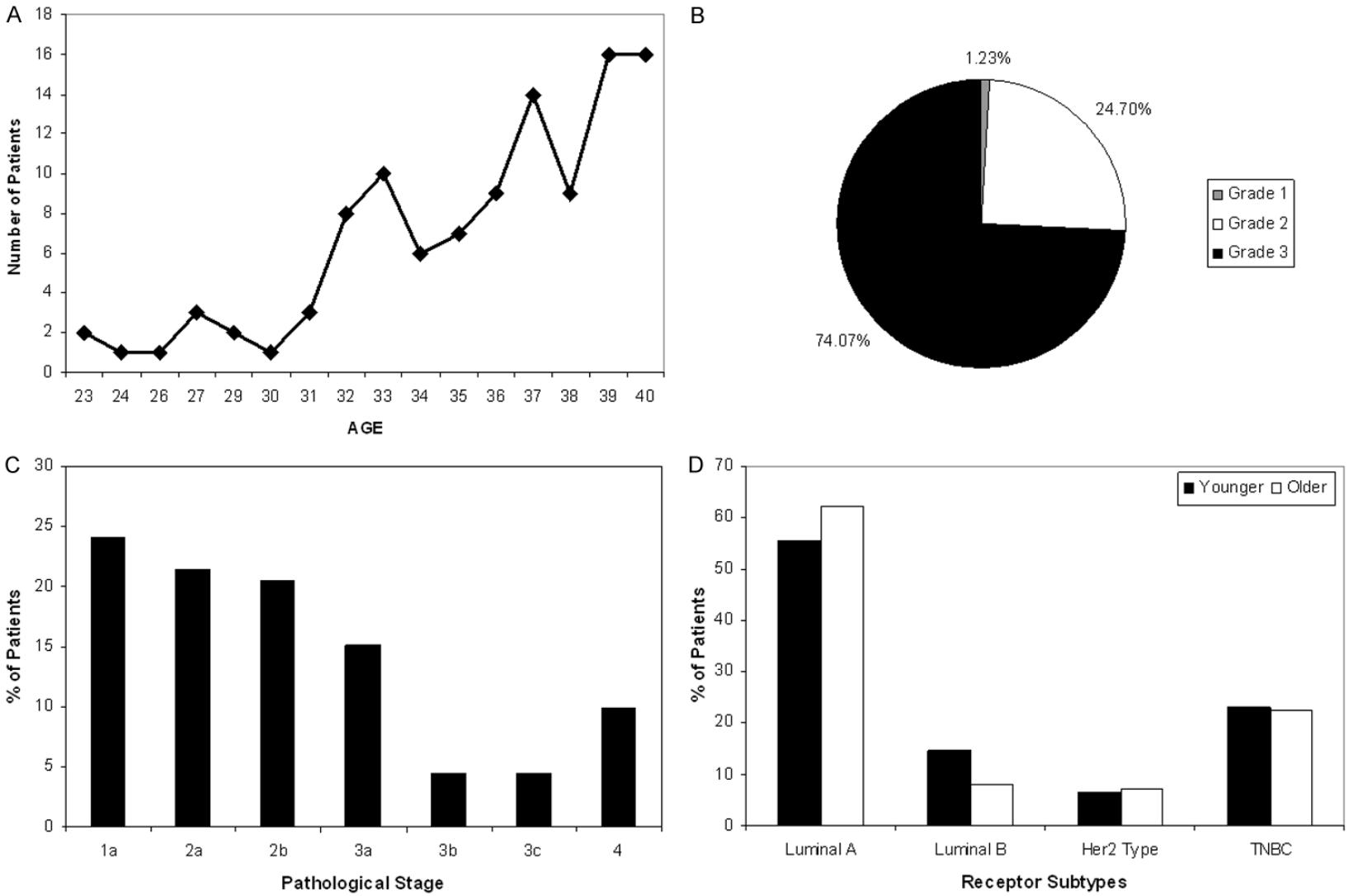

Figure 2. Clinical and pathological characters of early onset breast cancer in African American patients. A. Age distribution curve of the AA younger group. B. Distribution in AA younger group by Histological grade. C. Distribution in AA younger group by Pathological stage. D. Percentage of women in AA younger and older groups for each receptor subtype.

63% of NHW women were diagnosed with early stage primary tumors (Stage 1), which was the highest among all races. In the Indian younger group, this percentage was the lowest (10.1%). Contrastingly, cancers with stages 2 and 3 were most commonly observed in the younger Indian women (87.87%), followed by AA (66.05%), Chinese (62.42%), Hispanic (59.99%) and NHW women (35.64%). On a linear spectrum of pathological stage, the NHW women and Indian women were placed at the extremes, while the middle range was formed by AA, Hispanic and Chinese younger women. Although, a noticeable disparity existed between NHW and Indian women, there was no significant racial disparity observed among Chinese, AA and Hispanic younger women in terms of pathologic stage. However, upon analyzing patients with stage 4 or metastatic disease, we found that the AA younger group had the highest population (9.87%), followed by Hispanic (7.84%), Indian (2.02%), NHW (1%) and Chinese (0%) younger groups. Considering the larger size of the Chinese younger group database, a complete absence of metastases may suggest that younger Chinese women are least likely to present with BCa metastases at diagnosis. Prevalence of nodal metastasis also was highest in AA women (63.4%) followed by Indian (60.63%), Hispanic (50.59%), Chinese (40.78%) and NHW women (25.75%). These observations illustrate that younger AA, Indian and Hispanic women typically present with higher stage and tumor grade than their Chinese and NHW counterparts.

Characterization of BCa subtypes across races

BCa subtypes in NHW patients: In the younger group, the median age of women at diagnosis was 37 years and the average age was 35.72 years (**Figure 1A**). Information of tumor grade and pathological stage was available for 99 and 101 patients respectively. Distribution patterns are shown in **Figure 1B** and **1C**. Overall nodal metastasis in the younger group was 25.75% (n = 26) and was the lowest among all races. Classifications based on molecular subtypes in both age groups are shown in **Table 2**. Compared to the reference population (older group), the prevalence of Luminal A subtype was significantly ($p = 0.026$) reduced in younger women. Her2/neu over-expression subtype was observed to be similar in both age groups. However, prevalence of Luminal B subtype was significantly higher ($p = 0.0009$) and the overall HER2/neu expression was about two fold higher in the younger group ($p = 0.004$). The percentage of NHW women diagnosed with TNBC subtype was very high ($p = 7.56*10^{-6}$) in the younger group, as seen in **Figure 1D**, suggesting that older NHW women are less likely to have the TNBC subtype.

BCa subtypes in AA patients: In the younger group, the median age of women at diagnosis was 37 years and the average age was 35.54 years (**Figure 2A**). Information of tumor grade and pathological stage was available for 81 and 112 patients respectively. Distribution patterns are shown in **Figure 2B** and **2C**. AA younger group demonstrated the highest percentage of nodal metastasis (63.4%) among the younger groups across all races. Based on the molecular subtype classification shown in **Table 2**, compared to older group, the expression of Luminal A subtype was lower in younger AA women. Prevalence of Her2/neu over-expression subtype was similar in both age groups. Luminal B subtype presentation was significantly higher ($p = 0.014$) in the younger group. Although, the overall prevalence of ER+/PR+ BCa in the younger group was similar to that in the older group, the overall expression of Her2/neu receptor was about 30% higher in the younger group. However, it did not achieve the statistical significance ($p = 0.11$). Prevalence of TNBC subtype was similar in both age groups as seen in **Figure 2D**.

BCa subtypes in Hispanic patients: The median age at diagnosis of women in the younger group was 35 years and the average age was 34.35 years (**Figure 3A**). Information of tumor grade and pathological stage was available for 266 and 255 patients respectively. Distribution patterns are shown in **Figure 3B** and **3C**. Overall prevalence of nodal disease was 50.59% in the younger group. Based on the molecular subtype classification shown in **Table 2**, prevalence of Luminal A subtype was lower in younger group and of Luminal B subtype was similar in both age groups. Her2/neu over-expression subtype was significantly higher in the younger (11.4%) group than the older (6.47%) group. Similarly, prevalence of TNBC subtype was also significantly higher in the younger (22.77%) group than the older (14.70%) group as shown in **Figure 3D**.

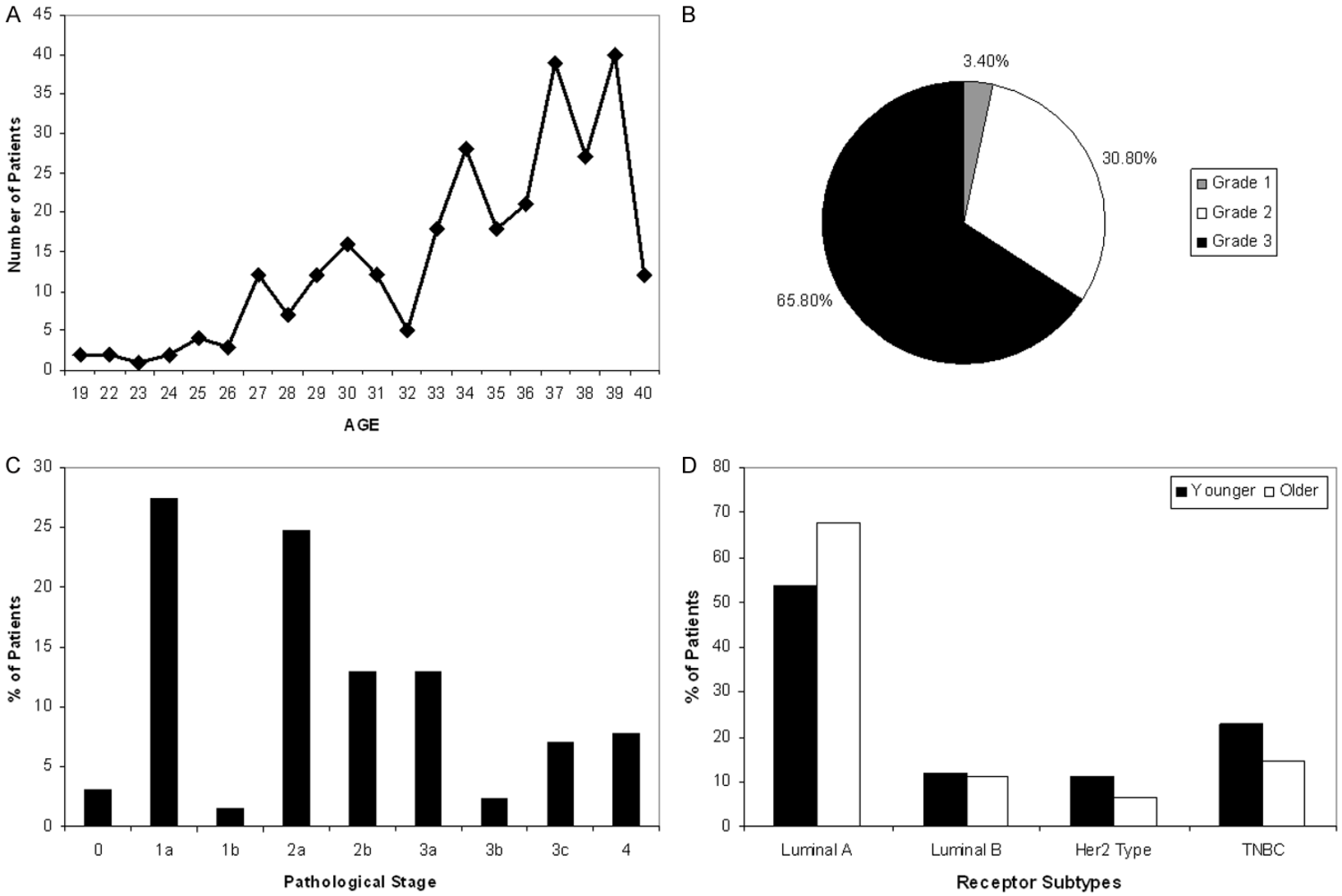

Figure 3. Clinical and pathological characters of early onset breast cancer in Hispanic patients. A. Age distribution curve of the Hispanic younger group. B. Distribution in Hispanic younger group by Histological grade. C. Distribution in Hispanic younger group by Pathological stage. D. Percentage of women in Hispanic younger and older groups for each receptor subtype.

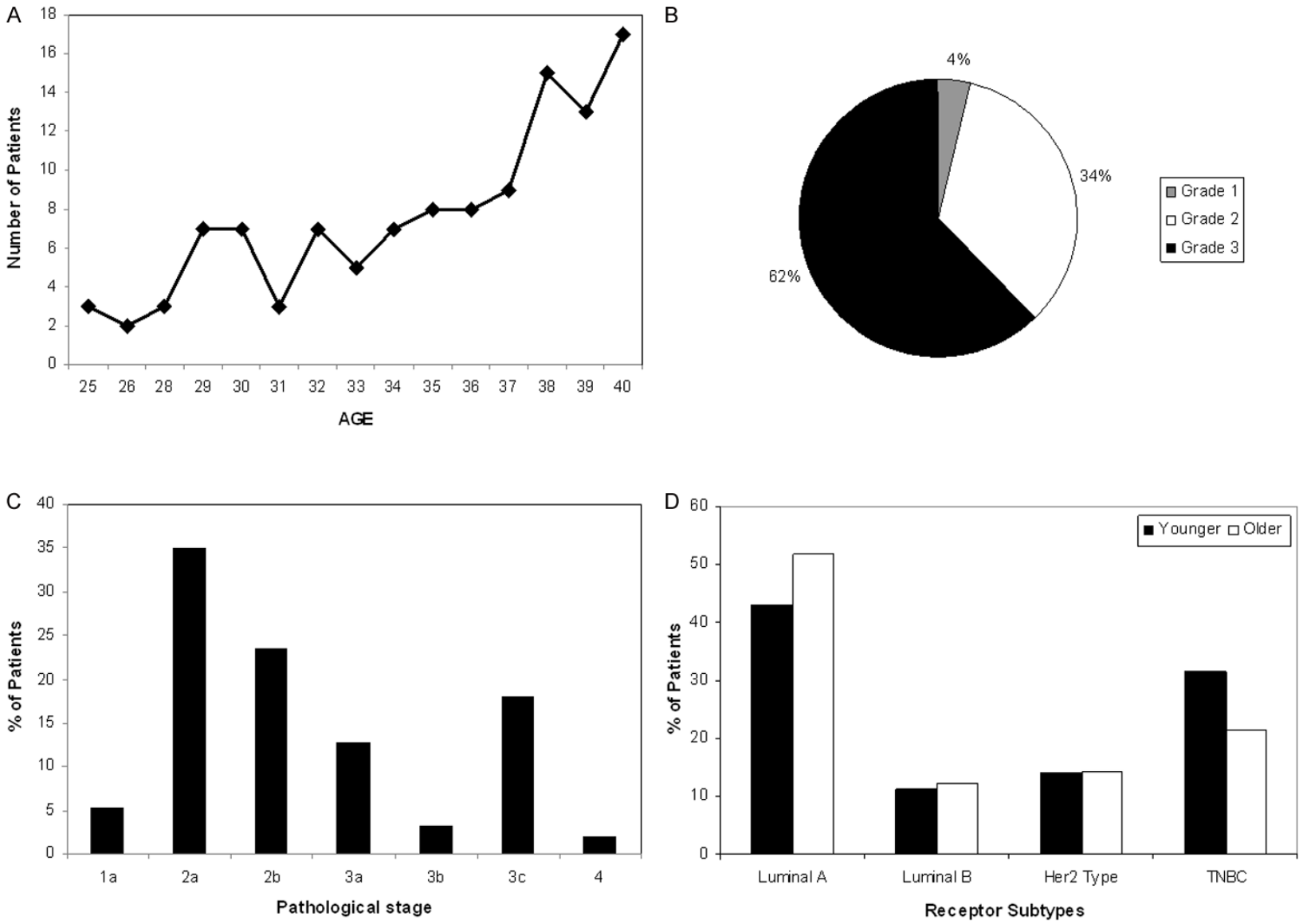

Figure 4. Clinical and pathological characters of early onset breast cancer in Indian patients. A. Age distribution curve of the Indian younger group. B. Distribution in Indian younger group by Histological grade. C. Distribution in Indian younger group by Pathological stage. D. Percentage of women in Indian younger and older groups for each receptor subtype.

BCa subtypes in Indian patients: Median age at diagnosis in the younger Indian group was 36 years and the average age was 35.10 years (**Figure 4A**). Information of tumor grade and pathological stage was available for 106 and 94 patients respectively. Distribution patterns are shown in **Figure 4B** and **4C**. Overall prevalence of nodal disease was 60.64% (n = 57) in younger group of Indian women. Based on the molecular subtype classification shown in **Table 2**, the Luminal A subtype population in the younger Indian group was the smallest among all races. Moreover, its prevalence was low in the entire Indian population. Consequently, no statistically significant variation (p = 0.19) was observed upon comparing the two age groups in the Indian population for the Luminal A subtype. Prevalence of both Luminal B and Her2/neu over-expression subtypes was marginally lower in younger group than the older group as shown in **Figure 4D**. Presentation of the TNBC subtype was observed in 31.57% (n = 36) women in younger group which was not only significantly higher (p = 0.02) than in the older group, but was the highest among all races.

BCa subtypes in Chinese patients: In the Chinese younger group, the median age at diagnosis and the average age were 38 years (**Figure 5A**). Tumor grade and pathological stage information was available for 153 and 228 patients respectively. Distribution patterns are shown in **Figure 5B** and **5C**. Overall prevalence of nodal disease was 40.78% (n = 93) in the Chinese younger group. Based on the molecular subtype classification shown in **Table 2**, prevalence of the Luminal A subtype was similar in both age groups. A significant rise (p = $6.5*10^{-9}$) of about 2.5-fold was observed in the Luminal B subtype in the younger group. Unlike the younger groups in other races, prevalence of the HER2/neu over-expression subtype was observed to be significantly lower (p = 0.04) in the younger group than in the older group. Surprisingly, the prevalence of TNBC subtype also was remarkably lower (p = 0.08) in the younger group than in older group as shown in **Figure 5D**. These observations were unique to Chinese women.

Receptor expression and molecular subtype disparities across races

Based on the analysis of study populations (younger group) with the mean of reference populations (older group) as seen in **Table 3** and Supplemental Figure 1, the prevalence of Luminal A subtype was significantly lower in younger Indian women (p = 0.0113). Among the other four races, no statistically significant disparity was observed. Prevalence of Luminal B subtype was significantly higher across younger AA, NHW, Chinese and Hispanic women. Statistically, this variation between the two age groups was highest among AA women (p = 0) followed by NHW (p = 0.0002), Chinese (p = 0.0003) and Hispanic women (p = 0.0128). Although, the variation observed in younger Indian women compared to the mean of the reference population was significant (p = 0.047), but in the Indian population subset, the Luminal B presentation was marginally higher in older group.

For the HER2/neu over-expression subtype, we did not observe a statistically significant variation in the younger group compared to the mean of the reference population in any of the races. However, upon reviewing total HER2/neu positive populations in both subtypes (Luminal B and Her2/Neu overexpression), significant disparities were observed across races. Indian, Hispanic and Chinese women in the younger group demonstrated significantly higher numbers of HER2/neu positive BCas than NHW and AA women. This variation was highest among Indian women (p = 0.0006) followed by Hispanic (p = 0.0099) and Chinese women (p = 0.053). Statistically, the variation was not significant for AA (p = 0.11) and NHW (p = 0.438) women. TNBC, known as the most aggressive phenotype, was more prevalent in the younger group populations across all races with the exception of Chinese. However, a statistically significant rise was observed only in younger Indian women (p = 0.0369), as shown in **Table 3**.

Discussion

The results of this study demonstrate that early onset BCa has distinct biological features in its clinical and pathological characteristics among racial groups. In previous studies [5-7, 45, 51], racial disparity was studied on ethnic groups identified solely in U.S. patient databases. The strength of our study was that in addition to examining 3 major racial groups in United States (AA, NHW and Hispanics), we also studied Indian and Chinese women (constituting

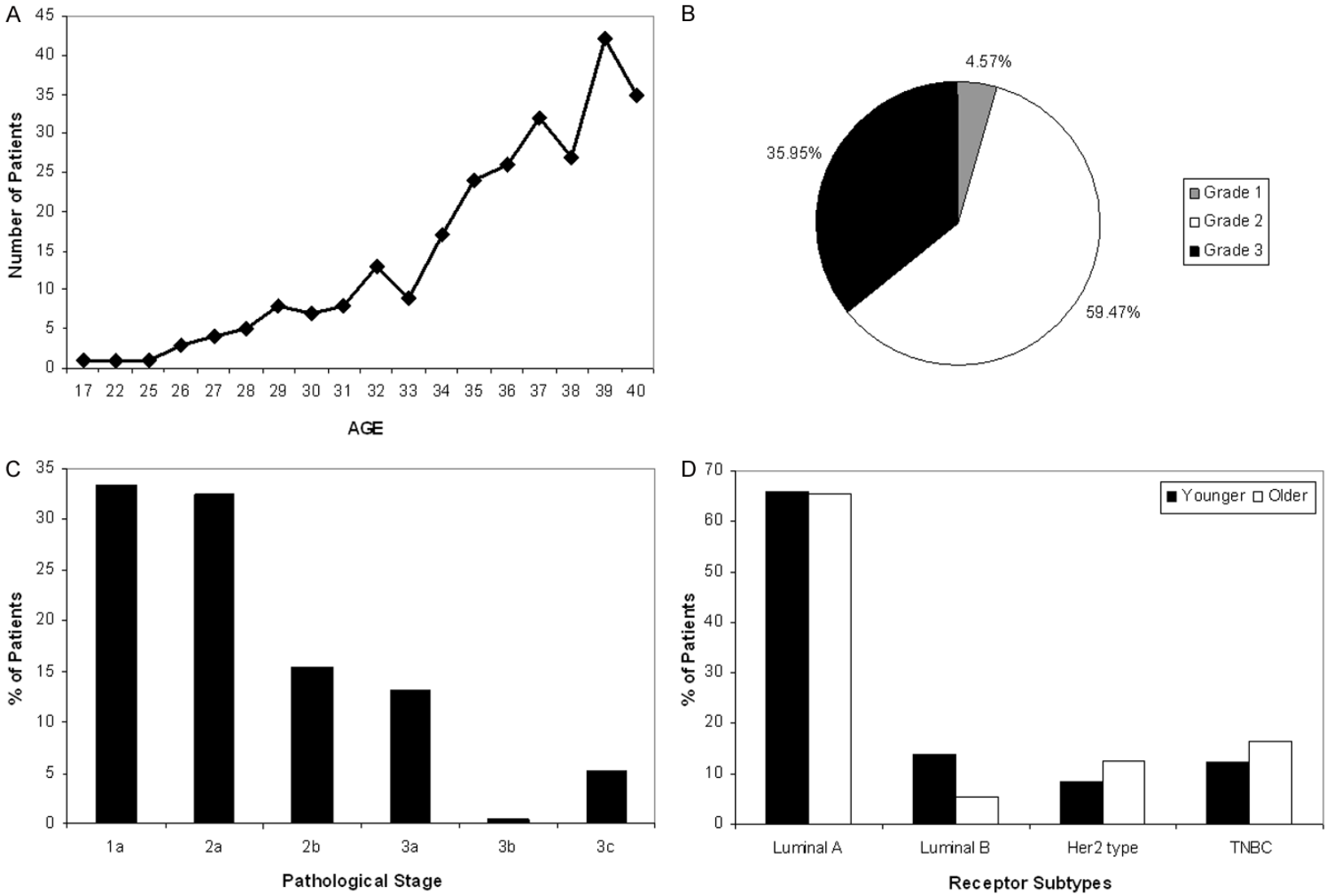

Figure 5. Clinical and pathological characters of early onset breast cancer in Chinese patients. A. Age distribution curve of the Chinese younger group. B. Distribution in Chinese younger group by Histological grade. C. Distribution in Chinese younger group by Pathological stage. D. Percentage of women in Chinese younger and older groups for each receptor subtype.

Table 3. Statistical analysis (*P* values)-Study population of each race with mean of reference population

	NHW	AA	Hispanic	Indian	Chinese
Luminal A	0.8129	0.2489	0.1760	0.0113	0.9760
Luminal B	0.0002	0.0000	0.0128	0.0468	0.0003
Her2 Overexpression	0.3174	0.4624	0.5051	0.1594	0.8420
TNBC	0.9561	0.3475	0.3747	0.0369	0.5804
Total Her2 Positive	0.4379	0.1103	0.0099	0.0006	0.0531

more than a third of the world's population) from their native origins.

A review of the statistical analysis (**Table 3**) strongly suggests that BCa in younger Indian women presents with significantly higher levels of HER2/neu expression and is more likely to be associated with the HER2/neu overexpression subtype. Furthermore, younger Indian women are at a significantly higher risk for the TNBC subtype and are least likely to present with the luminal subtypes. Results show that this disparity is maintained throughout the entire population of Indian women with BCa regardless of age, although it is more significant in the younger group.

Younger Chinese and NHW women are least likely to be diagnosed with TNBC among all races. Women in both of these racial groups were more likely to be diagnosed with BCa of the Luminal A subtype. In terms of HER2/neu expression, younger Chinese women expressed a significantly higher level of HER2/neu expression than their NHW counterparts. However, the disparity was largest when NHW women were compared with Indian women across all receptor subtypes in early onset BCa.

This study also demonstrated that among younger groups in both AA and Hispanic populations, the prevalence of Luminal A and TNBC subtypes are similar and higher than among NHW and Chinese women but lower than Indian women. For Luminal A subtype, it was vice versa. Hispanic women were more likely to express HER2/neu receptor protein in the absence of hormone receptor expression than the AA women. But it was not the same with Luminal B presentation. The study results showed that the prevalence of Luminal B subtype in AA younger group was marginally higher than in other races. The increased expression of the HER2/neu receptor seen in younger AA women was largely associated with the luminal presentation or hormone-positive BCa.

Recent studies on racial disparity that specifically focused on early onset BCa, showed a higher prevalence of TNBC in younger AA women [7, 30] than other races. These studies primarily compared AA women with NHW and Hispanic women. Although, the study by Clarke et al [30] also included the Asian younger group, however, the group was not defined adequately and included diverse ethnicities. Clarke et al [30] showed that younger Asian women are less likely to present with TNBC than younger NHW women. The source of data for most of the studies on racial disparity in BCa [5, 7, 8, 10, 30] was the California Cancer Registry (CCR), which included U.S. patients only. Certain studies which used the CCR database to include patients from the Asian group [19, 21, 22] have described their study populations as largely constituted by women of Chinese ethnicity.

It is important to understand that the term "Asian" which was used in many studies, encompassed a number of diverse ethnicities, and did not include the Indian ethnic group. Since the Indians appear sparsely in U.S. population databases, this group is often combined with other ethnic groups of Southeast Asia and the Chinese group to form the "Asian" group.

Some researchers have shown that Asian women are at higher risk for developing HER2/neu positive BCas compared to NHW women [18]. Kurian et al. identified the sub groups of Asian ethnicities [19] and showed that HER2/neu positive tumors are found most among Korean women (36%) followed by Filipina (31%), Indian/Pakistanis (29%), Chinese (26%), Hispanics (25%), AA (23%) and NHW women (19%). These results were shown in an age-adjusted population. For instance, if the Korean and Filipino group are excluded from the findings [19] of Kurian et al. (since they were not included in our study), the results of our study are similar. In contrast, some researchers have linked younger Asian women with BCa to lower expression of HER2/neu receptor [27].

Independently, studies have demonstrated that younger AA [13] and Indian [55] women with

BCa are associated with larger tumor size, higher grade, later stage at diagnosis, more nodal or metastatic disease and absence of hormone receptor expression. Our study uniquely compared both AA and Indian groups with NHW, and also with each other, to further quantify the existing racial disparity. Our results show that younger AA women are more likely to present with higher grade and increased nodal and distant metastasis than younger Indian women, and that the disparity is more remarkable between AA and NHW women than between Indian and NHW women in terms of tumor grade and stage. However, the disparity for TNBC is larger between Indian and NHW women than between AA and NHW women.

There were certain noticeable limitations in this study. One of them was the relatively small size of cohorts in each race. Further, the methodology used to determine tumor receptor expression was marginally distinct at each of the participating institutions. Another limitation was the variation at the data source. Although, the data for AA, NHW and Hispanic women was collected from the U.S. patient populations, the Indian and Chinese data represented native populations from the respective countries. Native Indians or Chinese women may differ from their immigrant counterparts in the United States or other countries. Previous studies have established a significant variation in BCa incidence and mortality rates across populations in developed and developing countries on the basis of lifestyle factors, reproductive history and socio-economic status [3, 9, 56-59]. A study by Moran et al. showed no significant variation of hormone receptor negative disease between Indian and NHW women in the United States [55]. However, another study using native Indian population demonstrated a very high prevalence of TNBC in native Indian women as compared to Western women [60]. Our findings are quite similar to those of the later since we also included a native Indian population for our study.

In future, it would be interesting to confirm our results with a large cohort in a prospective study. Also, it would be of great interest to investigate genome-wide differences in racial disparity in early onset BCa across races.

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Disclosure of conflict of interest

None to disclose.

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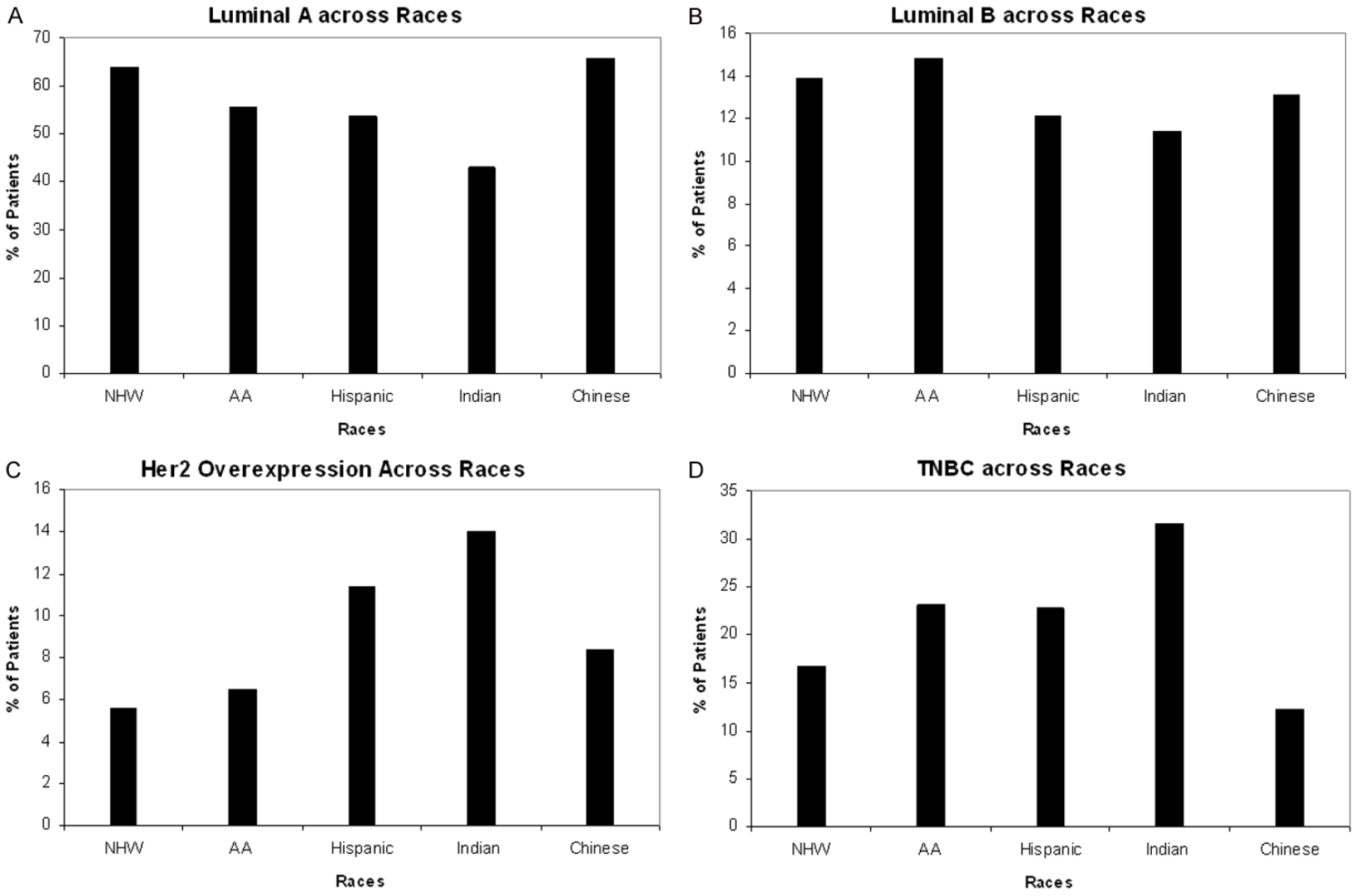

Supplemental Figure 1. Comparison of receptor subtypes across races in early onset breast cancer.