Molecular profiles and clinical-pathological features of Asian early-stage breast cancer patients

Margaret Chen[1], Ava Kwong[2], Carolyn Hendricks[3], Nina D'Abreo[4], Laura Lee[5], Hatem H. Soliman[6], Charles Cox[7], Heather M. Kling[8], Midas M. Kuilman[9], Rajith Bhaskaran[9], Shiyu Wang[8], Andrea Menicucci[8], Sarah Untch[8], William Audeh[8], FLEX Investigators Group

[1]ProHealth Care, Optum, UnitedHealth Group, Lake Success, NY; [2]University of Hong Kong, Hong Kong Hereditary Breast Cancer Family Registry, Hong Kong, Hong Kong; [3]Maryland Oncology and Hematology, US Oncology, Bethesda, MD; [4]NYU Winthrop Hospital, Mineola, NY; [5]Comprehensive Cancer Center, Palm Springs, CA; [6]Moffitt Cancer Center, Tampa, FL; [7]University of South Florida, Tampa, FL; [8]Medical Affairs, Agendia, Inc., Irvine, CA; [9]Research and Development, Agendia NV, Amsterdam, Netherlands

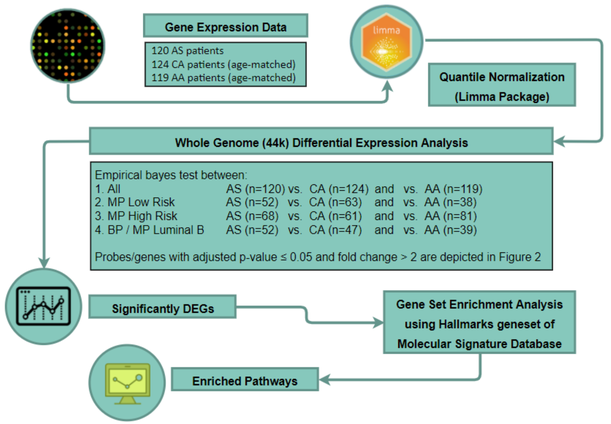
San Antonio Breast Cancer Symposium® - December 8-11, 2020 Poster #PS7-69

BACKGROUND

Breast cancer incidence in Asian populations has increased in recent years (1,2). Variation in prognosis and tumor subtypes indicates that further study is necessary to characterize these differences and identify actionable targets. Patients of Asian ancestry are underrepresented in US registries, and few studies have characterized tumors molecular profiles for these patients. In the current analysis, we assess clinical, pathological, and molecular profiles from self-reported Asian breast cancer patients (AS), in comparison with age-matched Caucasian (CA) and African American patients (AA), to evaluate the influence of Asian ancestry on differential gene expression in breast tumors.

METHODS

This meta-analysis included cohorts of self-reported AS, CA, and AA with early-stage, invasive breast cancer (EBC) prospectively enrolled in the US from 2011 to 2020 in FLEX (NCT03053193), MINT (NCT01501487), or IMPACt (NCT02670577) trials. AS were significantly younger (mean, 54 years) than CA (mean, 61 years, $p<0.001$) or AA (mean, 58 years, $p=0.002$); thus, an age-matched subset was selected for analyses. 70-gene signature (MammaPrint, MP), 80-gene signature (BluePrint, BP), and clinical-pathological features were compared among age-matched AS (n=124), CA (n=124), and AA (n=119). Whole-genome expression data were quantile normalized using R Limma package, and differentially expressed genes (DEGs) were compared among tumors of AS (n=120), CA (n=124), and AA (n=119). DEGs with adjusted (for false discovery rate <5%) p-value <0.05 and log2 fold change > 1.0 were considered significant.



CLINICAL CHARACTERISTICS

Table 1 Patient Characteristics *(*unknowns excluded)*

Patient Group	Age, Mean	Age, Median	Pre/Peri-Menopausal	Post-Menopausal
Asian (n=124)	54	54	35 (35%)	64 (65%)
Caucasian (n=3911)	61	62	701 (19%)	3000 (81%)
p-value	<0.0001		0.0001	
African American (n=467)	58	59	110 (26%)	319 (74%)
p-value	0.0024		0.06	

Tables 1-2. AS BC patients were significantly younger at diagnosis than CA and AA patients and more frequently pre/peri-menopausal compared with CA patients ($p<0.05$, **Table 1**), consistent with reports elsewhere (3). After adjusting for age, most clinical-pathological factors were similar between AS and CA patients (**Table 2**). Obesity prevalence was significantly lower in AS than in CA or AA, despite similar T2DM incidence, which is supported by diabetes studies in Asian American patients (4). Grade, nodal stage, and BP subtype distribution were also significantly different between tumors of AS and AA ($p<0.05$).

Table 2 Age –Matched Groups

Patient Characteristics *(*unknowns excluded)*	Asian (n=124)	Caucasian (n=124)	*p*-value	Asian (n=119)	African American (n=119)	*p*-value
Age, Mean	54	54	1.00	55	55	1.00
Age, Median	54	54		54	54	
Menopausal Status						
Pre/Peri	35 (35%)	44 (38%)		33 (34%)	28 (27%)	
Post	64 (65%)	73 (62%)	0.78	64 (66%)	75 (73%)	0.36
Grade						
G1	29 (26%)	38 (32%)		28 (25%)	26 (23%)	
G2	54 (47%)	59 (50%)		54 (49%)	38 (34%)	
G3	26 (23%)	17 (14%)		24 (22%)	45 (40%)	
GX	5 (4%)	5 (4%)	0.36	5 (4%)	4 (3%)	**0.025**
T stage						
T1	48 (57%)	52 (66%)		46 (57%)	43 (64%)	
T2	29 (34%)	24 (30%)		27 (34%)	21 (31%)	
T3	4 (5%)	2 (3%)		4 (5%)	2 (3%)	
T4	3 (4%)	1 (1%)	0.54	3 (4%)	1 (2%)	0.71
N stage						
N0	55 (68%)	62 (79%)		51 (66%)	48 (77%)	
N1	25 (31%)	14 (18%)		25 (33%)	10 (16%)	
N2/N3	1 (1%)	2 (2%)	0.21	1 (1%)	4 (7%)	**0.034**
Tumor Type						
IDC	98 (82%)	93 (79%)		94 (82%)	91 (81%)	
ILC	10 (8%)	16 (13%)		10 (9%)	14 (12%)	
Mixed IDC-ILC	4 (3%)	2 (2%)		4 (3%)	1 (1%)	
Other	7 (6%)	7 (6%)	0.54	7 (6%)	7 (6%)	0.48
MammaPrint Result						
Low Risk	53 (43%)	63 (51%)		50 (42%)	38 (32%)	
High Risk	71 (57%)	61 (49%)	0.25	69 (58%)	81 (68%)	0.14
BluePrint Result						
Luminal-type	106 (88%)	104 (92%)		103 (89%)	74 (66%)	
HER2-type	8 (7%)	2 (2%)		7 (6%)	7 (6%)	
Basal-type	6 (5%)	7 (6%)	0.17	6 (5%)	31 (28%)	**<0.001**
BMI Categories						
Underweight	4 (3%)	5 (4%)		4 (3%)	2 (2%)	
Normal weight	59 (51%)	34 (28%)	**<0.0001**	55 (49%)	7 (6%)	**<0.0001**
Overweight	43 (29%)	28 (23%)		34 (30%)	24 (21%)	
Obese	20 (17%)	55 (45%)		20 (18%)	83 (71%)	
Diabetes Status						
No evidence	90 (82%)	109 (92%)		86 (81%)	80 (74%)	
Type 1 DM	1 (1%)	0	**0.047**	1 (1%)	2 (2%)	0.445
Type 2 DM	19 (17%)	9 (8%)		19 (18%)	26 (24%)	

GENE EXPRESSION COMPARISON AMONG ASIAN, CAUCASIAN, AND AFRICAN AMERICAN PATIENTS

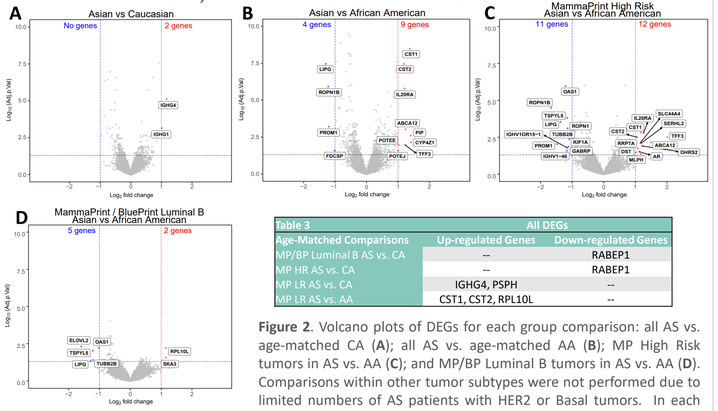


Table 3 All DEGs

Age-Matched Comparisons	Up-regulated Genes	Down-regulated Genes
MP/BP Luminal B AS vs. CA	--	RABEP1
MP HR AS vs. CA	--	RABEP1
MP LR AS vs. CA	IGHG4, PSPH	--
MP LR AS vs. AA	CST1, CST2, RPL10L	--

Figure 2. Volcano plots of DEGs for each group comparison: all AS vs. age-matched CA (**A**); all AS vs. age-matched AA (**B**); MP High Risk tumors in AS vs. AA (**C**); and MP/BP Luminal B tumors in AS vs. AA (**D**). Comparisons within other tumor subtypes were not performed due to limited numbers of AS patients with HER2 or Basal tumors. In each plot the number of DEGs upregulated in AS is shown in red, and downregulated genes are shown in blue. Comparisons with fewer than 4 DEGs are shown in **Table 3**.

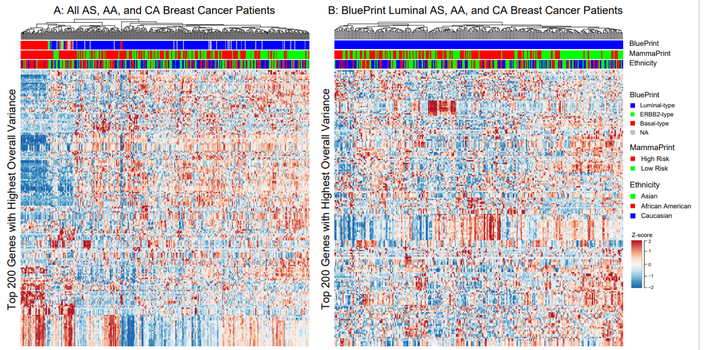


Figure 3. Hierarchical clustering of 200 genes with highest overall variance among tumors of age-matched AS, CA, and AA BC patients including all subtypes (**A**) or only BluePrint Luminal tumors (**B**). Each row represents 1 gene; each column represents 1 patient. Clustering demonstrates that MammaPrint High Risk, BluePrint Basal tumors, which are predominantly from patients of African ancestry, exhibit a distinct transcriptional profile. Clustering according to ethnicity/ancestry is not otherwise observed.

GENE SET ENRICHMENT IN ASIAN BREAST CANCER

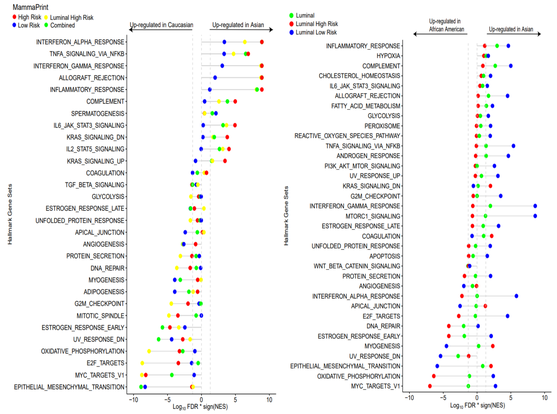


Figure 4. Gene set enrichment analysis results for tumors of AS vs. CA (left panel) and AS vs. AA (right panel, only BluePrint Luminal) patients. In each panel, pathways with upregulated genes in tumors of AS are displayed on the positive scale. Dashed lines indicate threshold for significance. Gene sets with significant regulation in at least one comparison are shown. Enriched gene sets upregulated in tumors of AS compared with CA are predominantly involved in immune response pathways; whereas enriched gene sets in BP Luminal tumors of AS vs. AA patients are involved in inflammation and cellular metabolism pathways.

CONCLUSIONS AND FUTURE DIRECTIONS

- The current analysis revealed different gene set enrichment patterns in tumors of AS compared with CA and AA, which may contribute to differential clinical outcomes and highlights the importance of including patients of Asian ancestry in genomic BC research. Upregulation of immune gene sets in AS patient tumors suggests that future studies utilizing immune cell deconvolution analysis may be informative.
- DEGs were greater in number and diversity in MP HR tumors between AS and AA than between AS and CA; however, further exploration of the underlying biological pathways is necessary.
- As genomic profiling data are not widely available for Asian American BC patients, further analyses including follow-up data are warranted to evaluate clinical outcomes and identify appropriate therapeutic strategies.

References

1. DeSantis et al. 2015. *Cancer Epidemiology, Biomarkers and Prevention*
2. Gomez et al. 2017. *Breast Cancer Research and Treatment*
3. Lin et al. 2019 *J Natl Cancer Inst*
4. Hsu et al. 2015 *ADA Diabetes Care*