Molecular profiling comparison of breast cancer subtypes in young women and older women

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INTRODUCTION

- Young women with breast cancer (YWBC; ≤40 years) have a more aggressive clinical course and younger age of diagnosis is associated with a poorer prognosis.[1]
- The genomic landscape of YWBC remains largely unknown with the exception of predisposing germline mutations in BRCA1/2 (11-23% of YWBC).[2]
- We assessed molecular profiling data to explore patterns of biomarkers that may provide insight into the aggressive biology observed in younger patients.

METHODS

- We explored molecular features in tumor subtypes of YWBC and older women with breast cancer (OWBC; ≥65 years).
- Somatic genomic profiles of 1879 breast tumors collected from 2013-2017 were assessed retrospectively and included in a de-identified data analysis if ER, PR and HER2 (immunohistochemistry [IHC] and/or in situ hybridization [ISH]) were available
- Testing included IHC, ISH and massively parallel sequencing assays (next-generation sequencing [NGS]) at a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ).
- Pearson's chi-square and regression analysis were utilized for comparisons and significance defined as $p < 0.05$.

RESULTS

Figure 1. Number of Patients in Age Groups

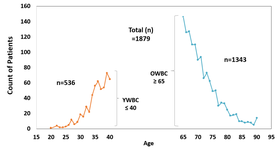
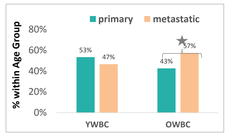


Figure 2. Disease Status by Age Group



- Disease status assigned according to specimen submitted for profiling. The frequency of metastatic specimens was significantly higher in OWBC ($\chi 2$=17.468, df=1, φ=0.098, p=0.000; OR 1.542, p=0.000).

Table 1. Breast Cancer Subtype by Age Group

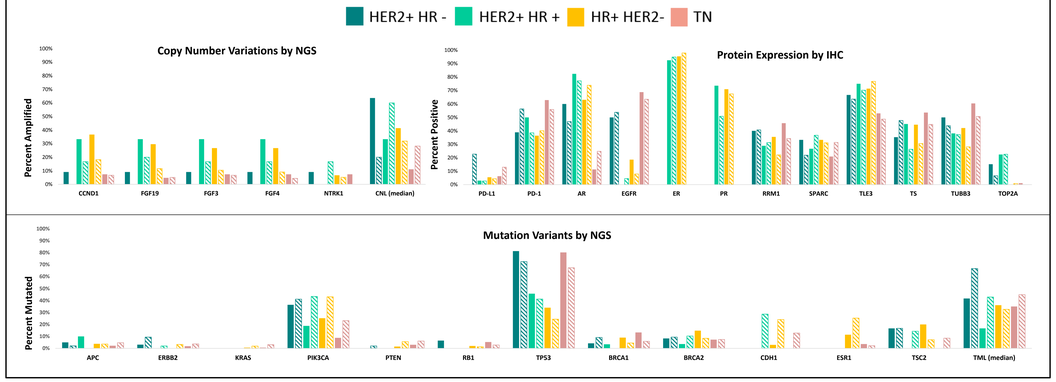
Breast Cancer Subtype	*Age Group* YWBC	OWBC	*Total*
HR+ HER2-	241	731	972
	24.8 %	75.2 %	100 %
	45 %	54.4 %	51.7 %
	12.8 %	38.9 %	51.7 %
HER2+HR-	37	67	104
	35.6 %	64.4 %	100 %
	6.9 %	5 %	5.5 %
	2 %	3.6 %	5.6 %
HER2+HR+	54	59	113
	47.8 %	52.2 %	100 %
	10.1 %	4.4 %	6 %
	2.9 %	3.1 %	6 %
TN	204	486	690
	29.6 %	70.4 %	100 %
	38.1 %	36.2 %	36.7 %
	10.9 %	25.9 %	36.8 %
Total	536	1343	1879
	28.5 %	71.5 %	100 %
	100 %	100 %	100 %
	28.5 %	71.5 %	100 %

Observed values are % within: subtype, age group, total

- **HR+ HER2-** breast cancers were the most frequently submitted for molecular analysis in both age groups

RESULTS

Figure 3. Differences in Biomarkers between YWBC (solid) vs. OWBC (striped) by BC Subtype



Biomarkers significantly different by Pearson's Chi-Square analysis (p<0.05 considered significant)

- There was higher PD-L1 expression in OWBC vs YWBC with HER2+ HR- tumors and TN tumors.
- PIK3CA mutations were more frequently observed in OWBC vs YWBC with HR+ HER2- tumors.
- There was a higher occurrence of CCND1, FGF19, FGF3, and FGF4 amplifications in YWBC vs OWBC with HR+HER2- tumors.

Table 2. List of Selected Biomarkers demonstrating significant differences between Y vs. O

Subtype	Biomarker/Assay	YWBC	OWBC	p-value
HER2+ HR-	PD-L1 IHC	0.0%	22.7%	0.009
HER2+ HR+	PR IHC	73.6%	51%	0.013
	APC NGS	10.0%	0.0%	0.03
	PIK3CA NGS	18.8%	43.4%	0.008
HR+ HER2-	AR IHC	63.1%	74%	0.002
	CCND1 CNV	36.7%	18.2%	0.042
	TP53 NGS	34.0%	24.4%	0.008
	FGF19 CNV	29.6%	11.6%	0.033
	FGF3 CNV	26.7%	10.4%	0.034
	FGF4 CNV	26.7%	9.1%	0.019
	PIK3CA NGS	25.2%	43.1%	4.00E-06
	EGFR IHC	18.6%	8%	0.004
	BRCA2 NGS	14.8%	8.4%	0.032
	BRCA1 NGS	9.0%	4.5%	0.047
	CDH1 NGS	2.9%	24.1%	0.006
	PTEN NGS	1.5%	5.6%	0.018
	ERBB2 NGS	0.0%	3.3%	0.008
TN	TP53 NGS	80.2%	67.4%	0.002
	BRCA1 NGS	13.3%	5.9%	0.015
	AR IHC	11.3%	25%	3.60E-04
	PIK3CA NGS	8.8%	23.2%	2.60E-05
	PD-L1 IHC	6.3%	13.0%	0.035
	CDH1 NGS	0.0%	12.8%	0.022

% positive (IHC); % amplified (CNV); % mutated, including pathogenic variants only

RESULTS

Table 3. Regression Analysis of Biomarker Differences between YWBC and OWBC by BC Subtype

			Total	Normal		Altered*			
				Y	O	Y	O		
	BC Subtype	Biomarker	n	n	n	(n) %	(n) %	Odds Ratio (OR)	P-value
CNV	HER2+ HR-	none							
	HER2+ HR+	none							
	HR+ HER2-	CCND1	107	19	63	(11) 37%	(14) 18%	-1.042	0.034
		FGF19	96	19	61	(8) 30%	(8) 12%	-1.210	0.034
		FGF3	107	22	69	(8) 27%	(8) 10%	-1.183	0.035
		FGF4	107	22	70	(8) 27%	(7) 9%	-1.323	0.022
	TN	none							
IHC	HER2+ HR-	none							
	HER2+ HR+	TS	109	29	42	(23) 44%	(15) 26%	-0.884	0.043
	HR+ HER2-	AR	945	87	185	(149) 63%	(524) 74%	0.538	0.001
		EGFR	364	79	246	(18) 19%	(21) 8%	-0.932	0.008
		ER	968	11	15	(227) 95%	(715) 98%	0.807	0.047
		RRM1	846	129	503	(71) 36%	(143) 22%	-0.660	0.000
		TS	918	123	483	(99) 45%	(213) 31%	-0.582	0.000
		TUBB3	676	103	358	(75) 42%	(140) 28%	-0.638	0.000
	TN	AR	683	180	361	(23) 11%	(119) 25%	0.930	0.000
		PDL1	458	133	275	(9) 6%	(41) 13%	0.790	0.039
		RRM1	578	89	272	(75) 46%	(142) 34%	-0.470	0.013
NGS	HER2+ HR-	none							
	HER2+ HR+	none							
	HR+ HER2-	BRCA2	502	137	356	(6) 4%	(3) 0.8%	-1.709	0.017
		PIK3CA	809	165	354	(50) 23%	(240) 40%	0.770	0.000
		TP53	749	139	416	(68) 33%	(126) 23%	-0.468	0.010
	TN	BRCA1	376	106	249	(15) 12%	(6) 2%	-1.782	0.000
		PIK3CA	609	169	336	(13) 7%	(91) 21%	1.244	0.000
		TP53	578	41	147	(132) 76%	(258) 64%	-0.608	0.003

- To control for disease status as a potential confounding factor (see Figure 2), a regression analysis was performed adjusting for metastatic disease. Biomarkers that were significantly different between YWBC vs. OWBC ($p<0.05$) are shown in Table 3, cells highlighted in orange indicate differences occurring with higher frequency in YWBC. *Altered = amplifications for CNV, positive expression for IHC and pathogenic mutations for NGS.

CONCLUSIONS

- There are distinct differences in the biology between young and older women with breast cancer.
- These molecular changes may contribute to increased understanding of breast cancer tumor biology and refinement of treatment strategies in younger and older women with breast cancer.

REFERENCES

1. Azim HA, et al. Genomic aberrations in young and elderly breast cancer patients. BMC Medicine. 2015;13:266.
2. Encinas G, et al. Somatic mutations in breast and serous ovarian cancer young patients: a systematic review and meta-analysis.Rev Assoc Med Bras. 2015; 61(5): 474-483.

QUESTIONS

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