Molecular landscape of HR+/HER2- male breast cancer (MaBC) compared with female breast cancer (FeBC)

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BACKGROUND

- Hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2−) breast cancer (BC) is more prevalent in male patients compared to female counterparts.
- Gender associated differences along with molecular differences, immune system, and other factors might play a crucial role in disease management.
- Here, we characterized molecular and immune differences between HR+/HER2- MaBC and FeBC.

METHODS

- 8156 female (HR+/HER2-, n = 5232) and 121 male (HR+/HER2-, n = 97) BC samples were analysed by next-generation sequencing (592, NextSeq; WES, NovaSeq) and Whole Transcriptome Sequencing (WTS; NovaSeq) (Caris Life Sciences, Phoenix, AZ).
- Tumor mutational burden (TMB) totaled somatic mutations per tumor (high>10 mt/MB).
- Microsatellite-instability (MSI) was tested by IHC and NGS.
- Immune cell fractions were calculated by deconvolution of WTS: Quantiseq.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q < 0.05).

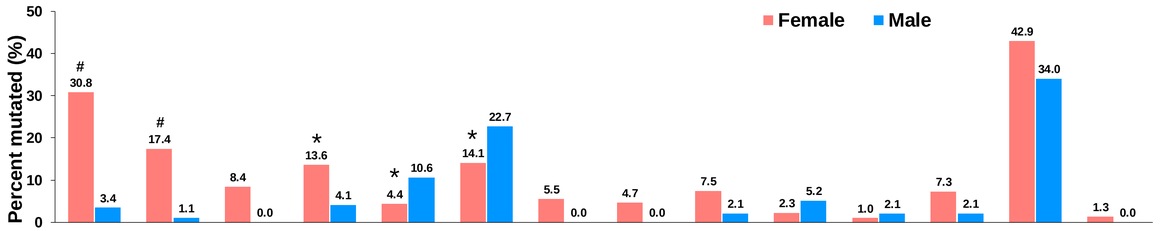
Table 1: Sample demographic information

		Female	Male
Count (N)		5232	97
Median Age [range]		62 [24 - >89]	67 [35 - >89]
Race	White	73.9% (3067/4151)	75.3% (61/81)
	Black/AA	16.4% (680/4151)	16.0% (13/81)
	Asian/Pacific Islander	4.0% (168/4151)	8.6% (7/81)
	Other	5.7% (236/4151)	0.0% (0/81)
Ethnicity	Not Hispanic or Latino	86.6% (3550/4097)	89.2% (66/74)
	Hispanic or Latino	13.4% (547/4097)	10.8% (8/74)

Race/ethnicity data is self-reported

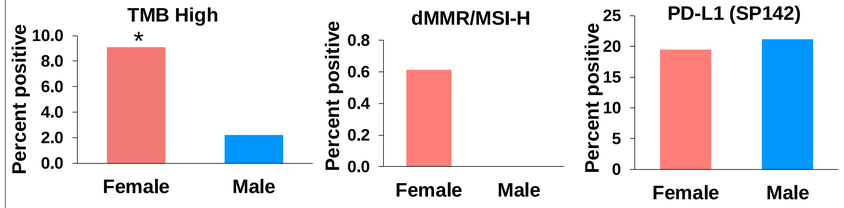
RESULTS

Figure 1. Mutation analysis of HR+/HER2− female breast cancer (FeBC) and male breast cancer (MBC)



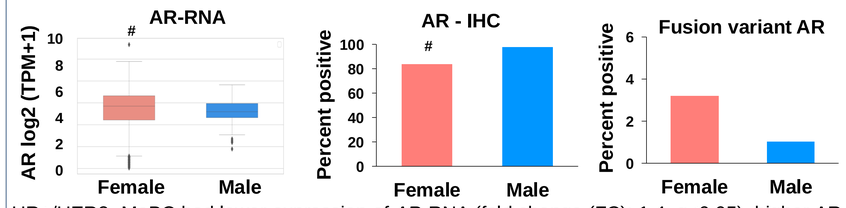
HR+/HER2- MaBC had higher frequency of *BRCA2* (10.64% vs 4.38%, p<0.05), *GATA3* (22.68% vs 14.11%, p<0.05), but lower frequency of *TP53* (3.45% vs 30.76%, q<0.05), *ESR1* (4.12% vs 13.62%, p<0.05) and *CDH1* (1.06% vs 17.43%, q<0.05) compared to HR+/HER2- FeBC. * p<0.05, # q<0.05

Figure 2. TMB-high, dMMR/MSI-H and PD-L1 positivity



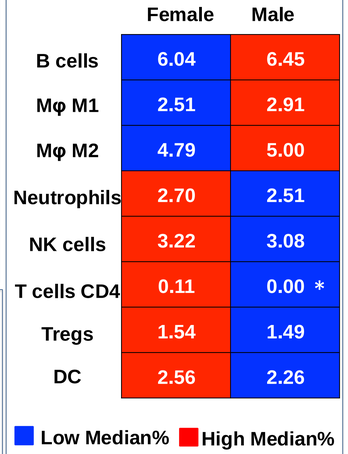
MaBC had lower frequency of TMB-high (2.2% vs 9.08%, p<0.05), but there was no difference in dMMR/MSI-high (0% vs 0.61%, p=1) or PD-L1 (IHC) positivity (21.21% vs 19.47%, p=0.72). * p<0.05

Figure 3. AR expression and fusion variant-AR



HR+/HER2- MaBC had lower expression of *AR*-RNA (fold change (FC): 1.4, q<0.05), higher AR-protein (IHC) positivity (97.94% vs 84.03%, q<0.05), but no difference was noted in the frequency of fusion variant-AR (1.04% vs 3.19%, p=0.37) compared to FeBC. # q<0.05

Figure 4. Immune cell infiltration



Female BC had increased infiltration of DC4 T cells (0.11% vs. 2.9%) compared to male BC. For monocytes and CD8 T cells median was 0 in both groups. *p<0.05.

Figure 5. Immune-related gene expression

	Checkpoint gene			MHC Class-I			MHC Class-II	
	Female	Male		Female	Male		Female	Male
FOXP3	1.89	1.93	*HLA-C*	155.11	189.39	*HLA-DRB1*	83.79	103.64
IDO1	0.99	0.79	*B2M*	1423.6	1444.6	*HLA-DQB1*	18.57	19.66
CD274	3.36	2.73	*TAP1*	10.85	11.08	*HLA-DPA1*	150.51	174.30
LAG3	0.92	0.82	*HLA-B*	136.18	163.4	*HLA-DPB1*	76.21	89.59
PDCD1	0.32	0.30	*HLA-A*	132.82	154.81	*HLA-DPB2*	0.05	0.04
HAVCR2	17.50	18.19	*TAP2*	25.17	23.90	*HLA-DQB2*	0.95	1.56 #
PDCD1LG2	1.14	1.24						
CTLA4	0.75	0.86						

Low TPM (Median) High TPM (Median)

MaBC had increased expression of MHC class I gene *HLA-B* (FC: 1.2), MHC class II gene *HLA-DQB2* (FC: 1.6). * p<0.05 # q<0.05

Figure 6. Cancer progression-related gene expression

	Stem cell genes			Drug efflux genes			Apoptosis-related	
	Female	Male		Female	Male		Female	Male
ALDH1A3	3.98	5.67	*ABCG2*	1.24	1.33	*BCL2L1*	28.14	28.01
ALDH1A1	9.19	5.99 #	*ABCC1*	22.68	21.17	*BIRC6*	99.80	90.57
NANOG	0.36	0.31	*ABCC2*	0.81	0.59 #	*NAIP*	18.69	20.57
PROM1	2.22	1.17 #	*FFAR4*	0.27	0.31	*BIRC2*	30.46	28.77
KLF4	7.18	5.26 #	*ABCC3*	12.14	10.10	*XIAP*	49.39	42.86
SOX2	0.30	0.21 #	*ABCB1*	2.85	2.78	*BCL2*	6.57	7.59
POU5F1	1.31	0.91 #				*BIRC3*	5.08	4.25

Low TPM (Median) High TPM (Median)

MaBC had decreased expression of drug efflux gene *ABCC2* (FC: 1.4), and stem cell genes (*KLF4, SOX2, POU5F1, PROM1, ALDH1A1*, FC: 1.3-1.9). # q<0.05

CONCLUSIONS

These data indicate that HR+/HER2- MaBC has a differential mutational spectrum and TMB-high frequency, immune cell infiltration, MHC Class I and MHC class II, drug efflux and stem cell-related gene expression compared to their HR+/HER2- FeBC counterparts. These suggest important differences in tumor biology between men and women with HR+/HER2- breast cancer. A better understanding of these differences with additional research may help in design future clinical trials and treatments for men with HR+/HER2- BC.