Molecular profiling identifies genetic heterogeneity in synchronous and asynchronous breast cancers

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Abstract

Background: Histologic heterogeneity of tumors is well documented; however, the molecular heterogeneity is not well understood, especially relative to driver mutations within clonal populations and their prognostic and predictive value.

Methods: Molecular profiling of breast cancers (BCs) at a single institution were analyzed for differences in clonal populations within the same breast, bilateral synchronous BCs, and/or within primary and paired locally recurrent or metastatic tumors. Gene alterations (GAs) were identified by next generation sequencing (NGS). GAs were compared in 9 synchronous BCs and 48 primary/recurrent paired BCs. Estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), were evaluated by immunohistochemistry (IHC). HER2 was evaluated by IHC and in situ hybridization (ISH).

Results: We identified GAs in 10 of 56 cases (18%); 2 were bilateral and 8 were paired primary/recurrent BCs. The 10 cases included 1 pair of separate primaries, 2 primary/locally recurrent, 2 primary/metastatic pairs, 3 metastatic pairs and 2 locally recurrent pairs. In the entire cohort, ER, PR, and HER2 status differed in 9 cases (16%), while AR status differed only in 4 (7%). 23% (13/56) were negative for ER, PR, and HER2 (triple negative [TN]); of 7 TN BCs with GAs in BCs, 6 of 7 (86%) were TN on both samples in the pair. *TP53* GAs were identified in 5 of the 10 cases (including the 2 synchronous), *PIK3CA* GAs were identified in 3 (1 synchronous), and *PTEN* GAs were identified in 4 (1 synchronous) cases. Other genes in which GAs appeared in only one of the pairs included *CDH1* (synchronous), *cMET* (asynchronous metastatic pair) and *KRAS* (primary/recurrent pair). Of the 2 synchronous cases, 1 had 2 and 1 had 3 different GAs in the bilateral BCs.

Conclusions: We identified that common GAs differ in both synchronous primary BCs and in paired primary/metastatic tissues. Such discordance could influence treatment recommendations. These findings highlight the molecular evolution of BC and the importance of evaluating predictive markers of treatment benefit both in synchronous and metastatic BCs.

Patient ER, PR, HER2, AR status and profile type

Figure 1. Distribution of cases by ER, PR, HER2 status

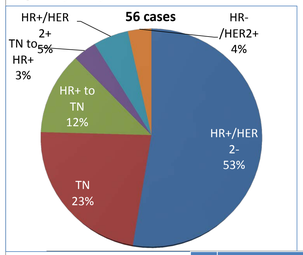


Table 1. Timing of profile and associated AR status by ER, PR, HER2 status. HR = hormone receptor

	# cases	Synchronous Cases	Cases with AR change*	Change in Gene Alterations
HR+/HER2-	29	7	4	3 (1 synch)
TNBC	13	0	0	6
HR+ to TN	7	1	0	1 (synch)
TN to HR+	2	0	0	0
HR+/HER2+	3	0	0	0
HR-/HER2+	2	1	0	0

*8 samples did not have AR tested

Table 3. Association of ER/PR changes with AR change

NC = no change
↑= HR goes from negative to positive
↓= HR goes from positive to negative
HR = hormone receptor

ER/PR	AR	# of cases
↑	↑	0
↑	NC	2
↑	↓	0
NC	↑	3
NC	NC	35
NC	↓	1
↓	↑	0
↓	NC	7
↓	↓	0

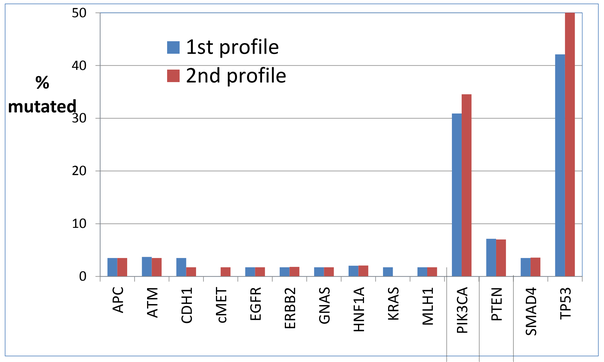
Not all cases had all three markers tested

Table 2. Details of changes in mutation and PTEN IHC
Information listed by case, including site of specimen profiled, time between specimen collections, and other associated information.

*HR = Hormone receptor
Pna = Specimen collected post neoadjuvant therapy

#	Subtype and AR status*	Specimen site	Specimen notes*	Time apart (days)	TP53 mutations with changes	PIK3CA mutations with changes	PTEN mutations with changes	Other mutations with changes	Genes with mutations but no change	PTEN protein status IHC
1	HR+/HER2-; AR-	Liver	Metastatic	245	WT	-	-	-	PIK3CA	Both positive
	HR+/HER2-; AR+	Liver	Metastatic		R249S, exon 7	-	-	-		
2	TN; AR-	Breast, left	Primary; pna	338	WT	-	-	-	-	Both negative
	TN; AR-	Chest wall	Local recurrence		R175H, exon 5	-	-	-	-	
3	HR+/HER2-; AR+	Breast, left	Local recurrence from left breast	0	WT	E545G, exon 9	-	-	-	Positive
	TN; AR+	Breast, right	Local recurrence, from left breast or new primary		V173fs, exon 5	WT	-	-	-	Negative
4	HR+/HER2-; AR+	Breast, right	Primary	0	WT	-	T319fs, exon 8	CDH1,c.1134_1137 +17 del exon 8	BRCA1, EGFR	Negative
	HR+/HER2-; AR-	Breast, left	Synchronous primary		R282W, exon 8	-	WT	WT		Positive
5	TN; AR-	Skin	Metastatic	174	WT	-	-	-	ATM	Both positive
	TN; AR-	Peritoneum	Metastatic		Q100X, exon 5	-	-	-		
6	TN; AR+	Breast, left	Primary; pna	504	-	WT	WT	-	TP53	Both positive
	TN; AR+	Breast, left	Axillary tail; local recurrence		-	E542K, exon 9	T319fs	-		
7	TN; AR-	Breast, left	Local recurrence, left breast	252	-	WT	L182V	-	TP53	Both positive
	TN; AR-	Breast, left	Local recurrence, left breast		-	C420R, exon 7	WT	-		
8	TN; AR-	Breast, left	Primary	491	-	-	WT	-	TP53	Positive
	TN; AR-	Lymph node	Left neck dissection		-	-	C304fs, exon 8	-		Negative
9	HR+/HER2-; AR+	Ovary	Metastatic	595	-	-	-	WT	PIK3CA	Both positive
	HR+/HER2-; AR+	Liver	Metastatic		-	-	-	cMET, T1010I, VUS, exon 14		
10	TN; AR-	Breast, left	Primary	106	-	-	-	KRAS, G13D	TP53, BRCA2	Positive
	TN; AR-	Soft Tissue	Metastatic		-	-	-	WT		Negative

Figure 2. Frequency of mutations. Shown by gene for paired samples.



Change from MT to WT	1	2
Change from WT to MT	2	2

# of cases

Conclusions

- Common GAs differ in both synchronous primary BCs and in paired primary/metastatic tissues and could influence treatment recommendations.
- These findings highlight the molecular evolution of BC and the importance of evaluating predictive markers of treatment benefit both in synchronous and metastatic BCs.
- Changes in androgen receptor are not dependent upon estrogen or progesterone changes.

References

1. Goswami, R, et al. Hotspot mutation panel testing reveals clonal evolution in a study of 265 paired primary and metastatic tumors. *Clinical Cancer Research* (2015) OF1-8.
2. Meric-Bernstam, F et al. Concordance of genomic alterations between primary and recurrent breast cancer. *Mol Cancer Ther (2014) 13(5) 1382-9.*
3. Millis et al. Predictive biomarker profiling of >6,000 breast cancer patients shows heterogeneity in TNBC, with treatment implications *Clinical Breast Cancer* (2015) in press.