Tumor profiling of 1168 geriatric breast tumors

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Abstract

Background: Breast cancer (BC) is a disease of aging and the number of geriatric patients is rising in the US. However, this group of patients is often excluded from clinical trials and under-represented in biomarker literature, complicating treatment selection strategies.
Methods: BC tumors referred to Caris Life Sciences (Phoenix, AZ) between 2009 and 2015 were tested with a combination of immunohistochemistry (IHC), fluorescent/chromogenic in-situ hybridization (ISH) and sequencing (Next-generation and Sanger). De-identified biomarker data were analyzed.
Results: A total of 1189 tumors collected from BC patients (M=21/F=1168) aged >=70 (range: 70-97, average 75.6) were analyzed (breast biopsy n=512; metastatic site n=677). Of the 1088 tumors with available IHCs of ER, PR and IHC and/or ISH of HER2, 613 (56%) were HR+/HER2-, 72 (7%) were HR+/HER2+, 346 (32%) were TNBC and 57 (5%) were HR-/HER2+. Overall, 39 of 47 genes sequenced carried mutations with frequencies ranging from 0.2% to 37%. Highest mutation rates were seen in PIK3CA (37%), TP53 (37%), BRCA2 (12%), PTEN (5.8%), AKT1 (4.2%), cMET (3.9%), ERBB2 (3.5%), BRCA1 (3.3%) and ATM (3.2%). Among 13 patients with ERBB2 mutation, 3 had it amplified. PD-L1 expression on tumor cells was seen in 13% and PD-1 expression on tumor-infiltrating lymphocytes in 46%, with TNBC subtype showing the highest expression: 20% and 60%, respectively. In addition, TOPO1, TLE3, AR, TOP2A, SPARC were overexpressed in 61%, 58%, 55%, 51%, 37% of tumors, respectively, suggesting potential sensitivity to irinotecan, taxanes, anthracyclines and nab-paclitaxel. TS, RRM1 and ERCC1 were under-expressed in 69%, 69% and 53%, respectively, suggesting potential sensitivity to fluoropyrimidines, gemcitabine and platinums. A comparison with 7531 tumors from patients younger than 70, as well as description of abnormalities per molecular subtype of BC are presented.
Conclusion: Using multiple testing technologies, potentially targetable biomarker aberrations were identified in a large cohort of geriatric tumors. Our study provides key elements for the design of clinical trials focusing on geriatric patient population.

Results (updated to reflect female patients only)

Figure 1: Patient Characteristics

Age Group	N	%
70-75	697	59.7%
76-80	283	24.2%
81-85	126	10.8%
86-90	47	4.0%
91-95	13	1.1%
96-100	2	0.2%
Total	1168	

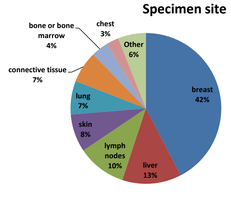
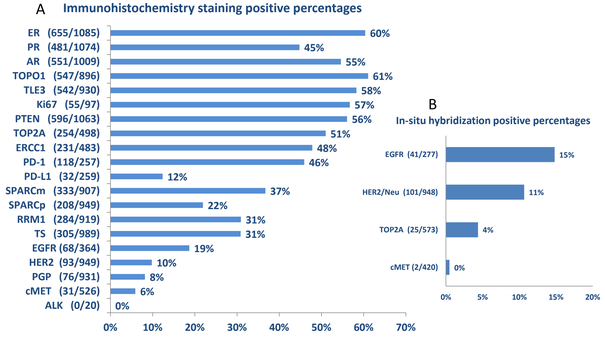
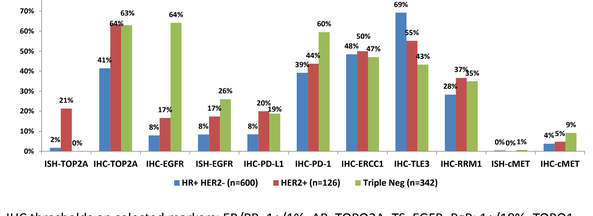


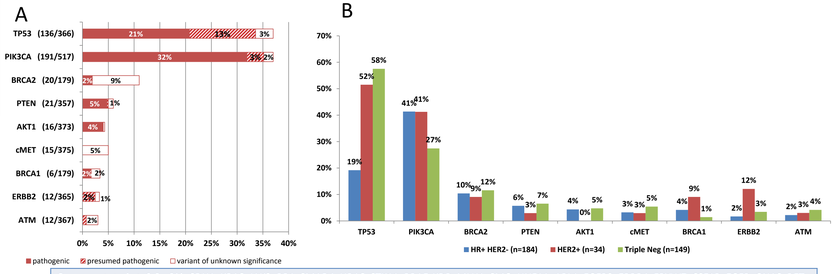
Figure 2: IHC and ISH biomarker frequencies in the geriatric cohort. A and B show the IHC and ISH markers in the complete geriatric cohort, while C shows selected IHC and ISH markers in the subgroups.





IHC thresholds on selected markers: ER/PR, 1+/1%; AR, TOPO2A, TS, EGFR, PgP: 1+/10%; TOPO1, TLE3, SPARC: 2+/30%; PTEN: 1+/50%; ERCC1: 2+/50% or 3+/10%; RRM1, cMET: 2+/ 50%, ALK: 3+/1%; Her2: 3+/10%. PD-L1 staining was read from the tumor cells (threshold 2+/5%) and PD-1 was read from tumor-infiltrating lymphocytes (1+/1%).
HER2 IHC and ISH grading is compliant with ASCO CAP guideline

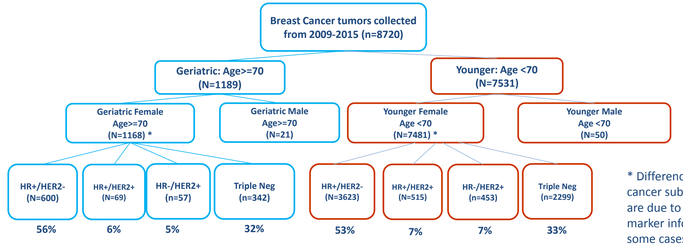
Figure 3: Mutation rates in the geriatric cohort. A shows the genes with mutation rates >2% in the complete geriatric cohort, while B shows the mutation rates in subgroups.



Genes mutated at 0.2 - 2%: CDH1, KRAS, JAK3, RB1, SMAD4, HRAS, STK11, BRAF, KDR, MLH1, SMO, HNF1A, ABL1, FGFR2, ERBB4, FBXW7, CSF1R, EGFR, GNAS, RET, PDGFRA, SMARCB1, MPL, PTPN11, JAK2, IDH1, FGFR1, CTNNB1, NRAS

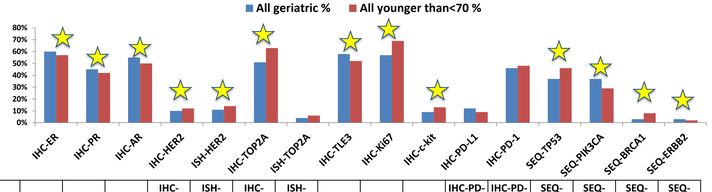
No mutations found in: ALK, CKIT, FLT3, GNA11, GNAQ, NOTCH1, NPM1, VHL

Figure 4: Comparison of the geriatric cohort with the younger cohort



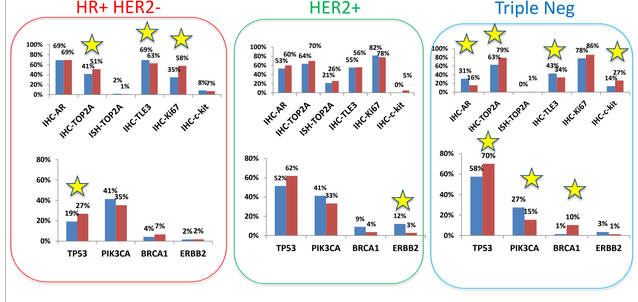
* Differences in breast cancer subgroup totals are due to lack of marker information in some cases

Figure 5: Comparison of selected markers between geriatric and younger cohorts.



	IHC-ER	IHC-PR	IHC-AR	IHC-HER2	ISH-HER2	IHC-TOP2A	ISH-TOP2A	IHC-TLE3	IHC-Ki67	IHC-c-kit	IHC-PD-L1	IHC-PD-1	SEQ-TP53	SEQ-PIK3CA	SEQ-BRCA1	SEQ-ERBB2
+	655	481	551	93	101	254	25	542	55	41	32	118	136	191	6	12
Total	1085	1074	1009	949	948	498	573	930	97	474	259	257	366	517	179	365
All geriatric %	60%	45%	55%	10%	11%	51%	4%	58%	57%	9%	12%	46%	0.37	0.37	0.03	0.03
+	3943	2876	3278	758	859	2142	234	3200	393	428	134	691	1071	977	83	38
total	6940	6928	6553	6134	6100	3419	3782	6178	571	3216	1464	1446	2317	3404	1086	2328
All younger than<70 %	57%	42%	50%	12%	14%	63%	6%	52%	69%	13%	9%	48%	0.46	0.29	0.08	0.02
P-values	0.0294	0.0462	0.0068	0.0242	0.0037	<0.0001	0.0883	0.0002	0.0259	0.0039	0.1103	0.5883	0.0013	0.0002	0.0393	0.0368

Figure 6: Comparison between geriatric (blue) and young (red) of selected markers by IHC or ISH (upper panels) and sequencing (lower panels) in HR+ HER2-, HER2+ and Triple Negative cohorts. Stars indicate p<0.05 by fisher-Exact test.



Conclusions

1. **In this sample, the most frequently positive IHCs included ER, PR, AR, TOPO1, TLE3, Ki67, PTEN, TOP2A**
   - ER, PR, AR, HER2 IHC results were similar in both age groups
   - Ki67 more often positive IHC in younger patient samples
   - AR IHC more often positive in older pats in TNBC only; other subgroups had similar frequency results, regardless of age
2. **The most frequently mutated genes were *TP53* and *PIK3CA***
   - *TP53* more often mutated in younger pats
   - *PIK3CA* more often mutated in geriatric pats
3. **TOP2A IHC more frequently positive among younger patients; amplification is overall low in both age groups, and almost exclusive of HER2+ patients**
4. ***ERBB2* was mutated in 12 cases of geriatric breast cancer and in 38 cases among younger patients**
5. **Only 1/69 geriatric TNBC samples (1%) had BRCA1 mutation, in comparison to 40/390 (10%) among younger patients with TNBC**
6. **PD-L1 in tumor cells tested positive in 8% HR+, 20% HER2+ and in 19% of TNBC geriatric patient samples**
7. **TILs were PD-1 positive in 39% HR+, 44% HER2+ and in 60% of TNBC geriatric patient samples**

References

1. Cancer Genome Atlas Network. "Comprehensive molecular portraits of human breast tumours." Nature. 2012 Oct 4;490(7418):61-70.
2. Jenkins, E.O, et. Al. 2014, "Age-specific changes in intrinsic breast cancer subtypes: a focus on older women." The Oncologist 2014;19:1076–1083