

Comparison of the mutational landscape of breast cancer during pregnancy and non-pregnant controls

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Background

Breast cancer during pregnancy (BCP) is a rare coexistence and is associated contradicting results about its biology and prognosis^{1,2}. Little is known about the impact pregnancy on breast cancer biology at the genomic level. Based mainly on class immunohistochemistry and mutational analysis in one small dataset^{3,4} it is believed that during pregnancy is biologically not different from breast cancer diagnosed outside pregnan

The aim of the study is to compare the pattern of somatic mutations between pregi and non-pregnant patients with breast cancer using a dataset of pregnant patients enrolled in BCP study and non-pregnant controls obtained from TCGA database.

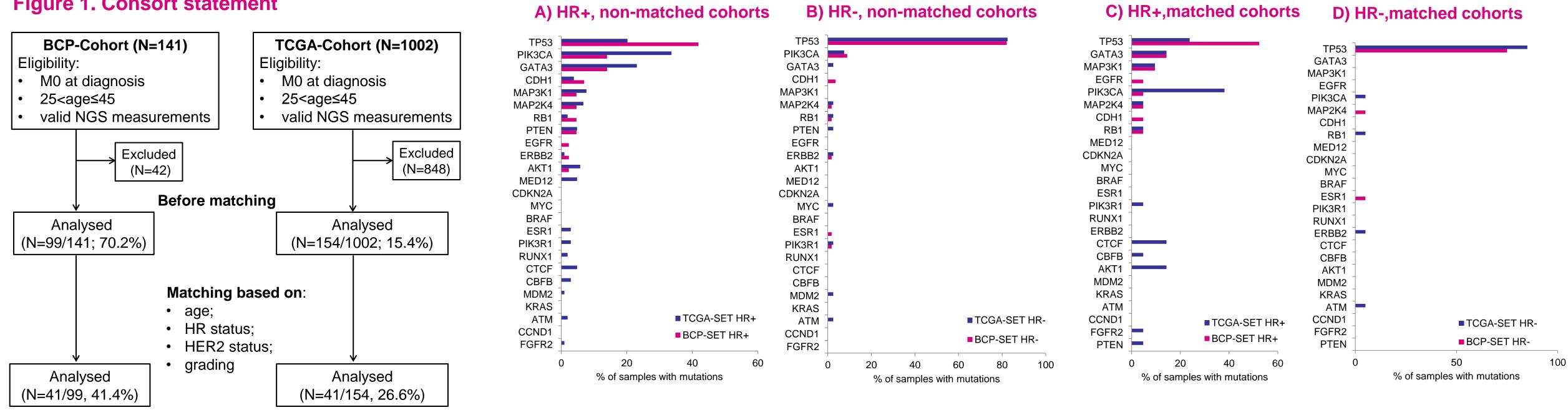
Materials and Methods

The BCP study (GBG 29; BIG 03-02) is a multicenter observational study for breast cancer during pregnancy. Formalin-fixed paraffin embedded (FFPE) core biopsies taken before therapy were retrospectively analysed for somatic mutations using an lon Torrent: Proton/PGM sequencing platform (Figure 1). The samples were assayed on a custom designed Breast Cancer Panel (BCPv2)⁵ that comprises 236 amplicons split into two primer pools and covers hotspot regions of 138 exons of 25 genes (Table 1). Raw data analyses were performed using the Ion Torrent Suite Software (version 4.4). Only non-synonymous mutations that have not been reported as being of germline origin were processed further. All statistical tests were by default 2-sided, significance level was set to α =0.05.

Table 1. Gene panel

BCPv2 Panel					
Genes	Exons	Amplicons			
GATA3	4-6	6			
PTEN	1-9	19			
FGFR2	3,7,12	3			
CCND1	1,3,4	3			
ATM	37	2			
KRAS	2-4	5			
MDM2	4,7,11	3			
RB1	2,3,8,13,14,16-18,20-22	12			
AKT1	3	1			
CBFB	3-5	3			
CTCF	3,4	5			
CDH1	2-16	29			
TP53	3-10	15			
MAP2K4	3-9	9			
ERBB2	7,8,14,17,19-21	9			
RUNX1	5-9	10			
PIK3CA	2,5,8,10,14,21	11			
MAP3K1	2-20	43			
PIK3R1	2-16	25			
ESR1	1,4,8	3			
EGFR	18-21	8			
BRAF	11,15	3			
MYC	2,3	3			
CDKN2A	1,2	4			
MED12	2	2			
25 Genes	138 Exons	236 Amplicons			

Figure 1. Consort statement

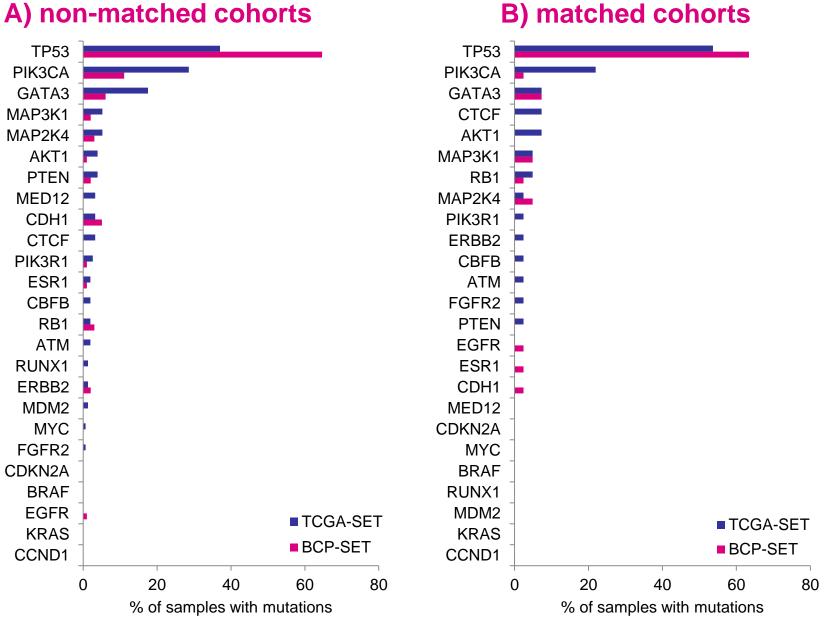


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Table 2. Clinical characteristics	in BCP vs.
non-pregnant controls	

		non-matched		matched	
Parameter	Category	BCP-cohort	TCGA-cohort	BCP-cohort	TCGA-cohort
Age, years	median	34	40	37	38
	min-max	26-43	26-45	28-43	26-45
Tumor size	T1-2	82 (82.8%)	130 (85.0%)	37 (90.2%)	34 (82.9%)
	T3-4	17 (17.2%)	23 (15.0%)	4 (9.8%)	7 (17.1%)
Nodal status	negative	48 (49.5%)	61 (39.6%)	23 (57.5%)	14 (34.1%)
	positive	49 (50.5%)	93 (60.4%)	17 (42.5%)	27 (65.9%)
Grading*	G1-2	30 (30.3%)	52 (49.5%)	12 (29.3%)	
	G3	69 (69.7%)	53 (50.5%)	29 (70.7%)	
HR*	positive	43 (43.4%)	104 (72.2%)	21 (51.2%)	
	negative	56 (56.6%)	40 (27.8%)	20 (48.8%)	
HER2*	positive	13 (13.1%)	24 (16.2%)	1 (2.4%)	
	negative	86 (86.9%)	124 (83.8%)	40 (97.6%)	



*Numbers in matched BCP-set vs.TCGA-set are identical by definition of the matching

Figure 3. Mutation patterns by HR status in BCP vs. non-pregnant controls

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Results

Figure 2. Mutation patterns overall in BCP vs. non-pregnant controls



- Comparison of the mutational patterns between BCP and nonpregnant controls (TCGA cohort) before any matching showed overall 102 mutations (average 1.03 mutations per samples) in BCP dataset vs. 195 (average 1.27 mutations per sample) in the TCGA. The most frequent somatic mutations for both cohorts were detected in TP53 (65% vs. 37%), PIK3CA (11% vs. 29%) and GATA3 (6% vs. 18%; Figure 2).
- Exact matching (1:1) in BCP and TCGA cohorts was performed based on age (26-30 vs. 31-35 vs. 36-40 vs. 41-45), HR (positive vs. negative), HER2 (positive vs. negative) and grading (G1/2 vs. G3) and yielded 41 patients from both datasets (Table 2).
- In the matched cohorts BCP patients had significantly less frequently N+ tumors as compared to non-pregnant controls (p=0.046) with no significant difference for TP53 (p=0.502) and GATA3 (p=1.000) mutational status whereas PIK3CA mutations were detected in only 2.4% of the pregnant patients vs. 22.0% of the non-pregnant controls (p=0.015; Figure 2). Within HR subgroups, overall TP53 was the most frequently mutated gene with higher mutational rate in HR-negative subgroup (52.4% vs. 75.0% for BCP; 23.8% vs. 85.0% for TCGA control; Figure 3).

Conclusions

Overall the mutational landscape does not seem to be different pregnant patients and no-pregnant controls The between imbalances in PIK3CA mutational rate after matching might be explained by a remaining bias caused by differences in sensitivity or specificity of methods used to detect mutations or differences in variables not used for matching. Further comparisons using other datasets, looking into gene expression patterns are currently conducted.

References

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