Associations of p21 gene functional polymorphisms with early-stage breast cancer clinicopathologic features and prognosis

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Objective

p21 plays multiple functions in cell cycle arrest, apoptosis and transcriptional regulation. Higher expression of p21 facilitates breast cancer (BC) progression and metastasis. Functional single nucleotide polymorphisms (SNPs) in *p21* gene have influence on p21 production and therefore are potential breast cancer prognostic biomarkers. The aim of the tis study was to evaluate the associations between functional SNPs in the *p21* gene with the early-stage breast cancer clinicopathologic features, locoregional and distant disease progression.

Methods

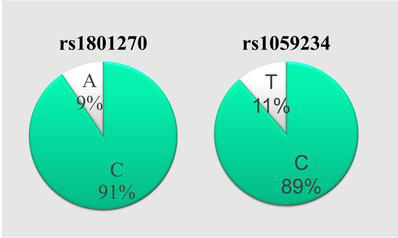
Patient inclusion criteria:
- Stage I-II BC (TNM: T1N0; T2N0; T1N1; T2N1);
- >18 year old;
- No serious comorbidities;
- Signed informed consent (protocol number BE-2-10).

Polymorphism selection:
- Located in P21 gene;
- Minor allele frequency >0.2;
- Functional

Genotyping:
- Genomic DNA was extracted from peripheral blood leukocytes;
- TaqMan genotyping assays were used.

Statistical analysis:
- Allelic SNP analysis model was performed;
- Fisher's exact test was used to analyse associations between clinicopathologic variables and SNPs;
- Survival differences were analysed using Kaplan-Meier log-rank and Cox proportional hazards models (univariate and multivariate; Multivariate analysis was adjusted for age, tumour size, lymph node status, grade, ER, PR and HER2 status).

Survival endpoints:
- Baseline time for survival – primary biopsy date;
- **Locoregional recurrence-free survival (LRFS)** – time from baseline to any first recurrence in ipsilateral breast or regional lymph nodes;
- **Metastasis-free survival (MFS)** - time from baseline to any first distant metastases.



Analysed polymorphisms and their allele distribution

Results

202 patients involved;

Primary treatments included:
- surgery (100%);
- chemotherapy (77%);
- hormone therapy (71%);
- trastuzumab (19%);
- radiation therapy (97%).

Variable		Frequency
Age at diagnosis	<50 years	65%
	≥50 years	35%
Tumour size	<2 cm	64%
	2-5 cm	36%
Lymph node status	Positive	55%
	Negative	45%
Grade (G)	G1 and G2	78 %
	G3	22%
ER status	ER positive	68%
	ER negative	32%
PR status	PR positive	60%
	PR negative	40%
HER2 status	HER2 positive	19%
	HER2 negative	81%

Frequency data for clinical and tumour biological factors.

Associations of SNPs with clinicopathological variables:

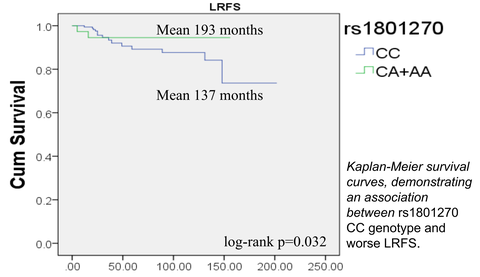
- No associations between SNPs and age at diagnosis, differentiation grade, ER, PR and HER2 status.
- Associations of SNPs with tumour size and lymph node status presented in the table below.

SNP	Genotype	Tumour size (<2 cm vs ≥2-5 cm) OR (95%CI)	p	Lymphnode status (positive vs negative) OR (95%CI)	p
rs1801270	CC vs CA+AA	2.79 (1.16-6.72)	0.022*	2.35 (1.04-5.29)	0.041*
	AA vs CA+CC	0.96 (0.41-1.73)	0.644	1.66 (0.49-1.86)	0.604
rs1059234	CC vs CT+TT	2.66 (1.10-6.44)	0.034*	1.45 (0.19-1.57)	0.060
	TT vs CT+CC	1.63 (0.87-1.83)	0.728	1.72 (0.82-1.78)	0.672

*Associations of SNPs with tomour size and lymph node status; * Significant associations*

Survival analysis:

- In univariate Cox regression analysis rs1801270 CC genotype carriers (vs CA+AA) had worse LRFS (HR 3.79; 95%CI 1.02-14.14; p=0.047). In multivariate model borderline statistical significance of this association remained (HR 2.33, 95%CI 0.99-9.60; p=0.05)
- No other significant associations were observed.



Kaplan-Meier survival curves, demonstrating an association between rs1801270 CC genotype and worse LRFS.

Conclusions

Functional polymorphisms in p21 gene may help to identify patients with more aggressive breast cancer phenotype. Furthermore, p21 rs1801270 SNP might contribute to the identification of early-stage breast cancer patients at higher risk for development of local recurrence. Further investigations with larger sample sizes are needed to confirm our findings.

Key words

P21, breast cancer, prognosis, SNP.