Analysis of *SIPA1* and *RRP1B* Gene Variants and Their Association with the Course of Cervical Cancer

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Objective

The signal induced proliferation associated gene 1 (*SIPA1*) is a gene that modifies the onset of metastases, that activates GTPases (proteins that catalyze the hydrolysis of guanosine triphosphate), is involved in mitogen-induced cell cycle regulation, may enhance or stop cell cycle progression and plays an important role in regulating cell adhesion. Ribosomal RNA processing 1 homolog B (*Rrp1b*) interacts with *SIPA1* and thus contributes to the regulation of the metastatic process. According to the literature, relationships between single nucleotide polymorphisms (SNPs) of these genes and tumor spread to regional lymph nodes in other oncological diseases have been identified, but their significance for cervical cancer as one of the most common oncological diseases progression is still poorly understood.
We performed a study to investigate the distribution of *SIPA1* gene functional polymorphisms (rs746429, rs931127) and *RRP1B* gene polymorphism (rs9306160) in a group of patients with cervical cancer. Then we analyzed the correlations between genotypes and alleles with tumor pathomorphological parameters and course of the disease.

Methods

- 172 patients with cervical cancer were enrolled in the retrospective study.
- Subjects were recruited from October 2014 to August 2020.
- Clinical data on patients and peritheral blood sample were collected.
- Genomic DNA was extracted from leucocytes.
- Molecular genetic studies were performed using the real time polymerase chain reaction method.
- The obtained SNPs were used in further statistical analysis in genotype and allelic models.
- The statistical analysis was performed using SPSS.

The associations between the genotypes and alleles with tumor characteristics were assessed using Pearson's Chi-square or Fisher's Exact tests.
Univariate and multivariate analysis to present odds ratios with 95% confidence intervals (CIs) and p-values were calculated with logistic regression.
Differences in PFS and OS were assessed using hazard ratios (HRs) from univariate
and multivariate Cox proportionate hazard models. p-value of <0.05 was considered statistically significant for all analysis.

Results

- 172 patients (mean (+/- SD age, 55.4 (+/- 13.5), 71.5% ≤50 years) were involved in the study.
- The distribution of genotypes was according to the Hardy-Weinberg equilibrium.

Figure 2. rs746429, rs9306160 *genotype distribution:*

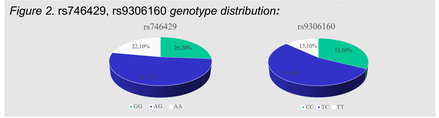
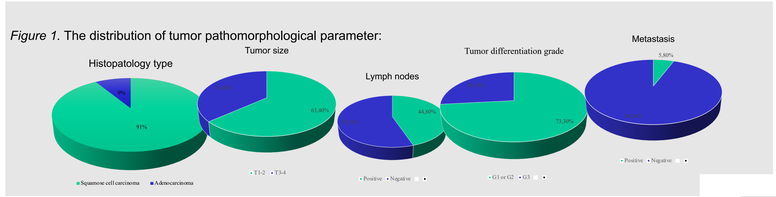
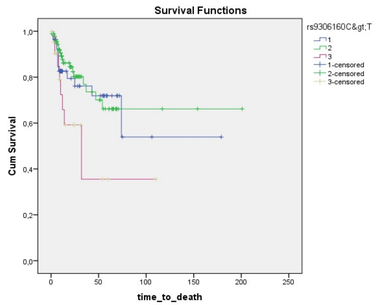


Figure 1. The distribution of tumor pathomorphological parameter:



- Data showed that rs746429 AG genotype compared to GG genotype decreased risk for bad differentiated (G3) tumors
(OR = 0.329, 95% CI: 0.147-0.736, p = 0.007). Patients with A allele were less likely to have G3 cancer (OR = 0.424, 95% CI: 0.205-0.880, p = 0.021).
AG genotype reduced the chance of having a worse prognosis (T3-4 and G3) cancer (OR = 0.255, 95% CI: 0.088-0.739, p = 0.012).
Carrying the A allele statistically significantly reduced the chance of having T3-4 and G3 cancer (OR = 0.296, 95% CI: 0.114-0.769, p = 0.012).
- In case of rs931127, no significant link between genotypes or alleles and tumor phenotype or patient survival (PFS or OS) was detected.
- Rs9306160: borderline significant association detected between TT genotype and metastases. Patients with TT genotype compared to CC genotype are more likely to have chance for metastases (OR = 5.889, 95% CI: 0.993-34.906, p = 0.051).
In a multivariate analysis this association remained significant when the adjustment for age of patients was done (OR = 6.356, 95% CI: 1.046-38.619, p = 0.045).
C allele was significantly associated with decreased risk for metastases (OR = 0.194, 95% CI: 0.057-0.661, p = 0.009). In cox regression analysis no significant link between genotypes or alleles and PFS was detected.
There was significant link between genotypes and OS (Log Rank, p = 0.048). Patients with TT genotype had shorter OS than CT genotype holders (Log Rank, p = 0.012),
but in a multivariate cox regression analysis no significant link between genotypes or alleles and OS was detected when the adjustment for tumor T, N, G and age of patients were done.

Figure 3. Kaplan_Meier curves for OS according to Rs9306160 *genotypes.*
Patiens with TT genotype showed a trend for shorter OS. Log Rank, p-value = 0.012. (1=CC, 2=CT, 3=TT)



Conclusions

Our study suggests that SNPs rs746429, Rs9306160 may have the potential to be markers contributing to the assessment of the cervical cancer phenotypes and survival prognosis.

Key words

Cervical cancer, SNPs, *SIPA1, RRP1B,* associations