The Investigation of Associations between Glutathione-S-Transferase Gene Polymorphisms and Cervical Cancer Prognosis

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Objectives

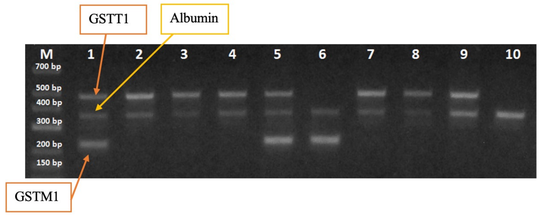
Cervical cancer is one of the most common cancers among woman worldwide. Literature reviews suggest that specific genetic variants coding for enzymes could be responsible for increased diseases susceptibility and could modify the course of disease.

Glutathione-S-Transferase, which is a detoxifying enzyme protecting human cells and DNA, is commonly suggested to influence cancer diseases. Null alleles mutations (*GSTM1*0* and/or *GSTT1*0* alleles) result in complete absence of the enzymes leading to a disabled detoxification of toxins and carcinogenic waste.

Therefore, we aimed to identify the distribution of genetic *GSTM1* null and *GSTT1* null polymorphism among cervical cancer patients and find possible correlations of these mutations with clinicopathological characteristics and disease prognosis.

Methods

Our study involved 172 women from Lithuania with cervical cancer. The mean age of participant was 55 years (between 22 and 82 years). Genomic DNA for GST analysis was extracted from blood leukocytes. Multiplex PCR was used to detect *GSTM1* and *GSTT1* null genotypes. Relationships between genotypes and cervical cancer clinicopathological features were estimated by Pearson's Chi-square/ Independent T test. Clinicopathological factors evaluated included TNM status (T, lymph node involvement, metastasis), tumor grade, the fact of cancer progression and death. Odds ratio was calculated by Logistic Regression. Survival prognosis was estimated by Kaplan-Meier and Cox Regression methods. SPSS was used to perform statistical data analysis. The data was collected from medical records.



PCR products of GSTM1 and GSTT1
From left to right, lane M - DNA molecular marker GeneRuler Low Range DNA Ladder (Thermo Fisher Scientific Baltics, Lithuania); lanes 1 and 5 indicate GSTT+ and GSTM+; lanes 2-4, 7-9 indicate GSTM1 null, GSTT1 present; lane 6 demonstrates GSTM1 present, GSTT1 null; lane 10 shows GSTM1 and GSTT1 null

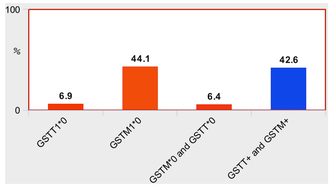
Clinicopathological features	N	%
Age		
20-40 years	24	13.9
40-60 years	79	45.9
60-90 years	69	40.2
Differentiation grade (G)		
G1	13	7.5
G2	113	65.7
G3	45	26.8
Patological tumor size (T)		
T1	26	15.2
T2	84	48.8
T3	59	34.3
T4	3	1.7
Pathological lymph node (N)		
N0	95	55.3
N1	77	44.7
Metastasis (M)		
M0	162	94.2
M1	10	5.8
Progression		
No	121	70.4
Yes	51	29.6
Deaths		
Alive	132	76.7
Dead	40	23.3

Characteristics of analyzed clinicopathological factors among cervical cancer patient group

Results

1. The distribution of studied genotypes was as follows:

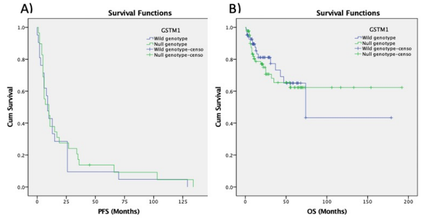
Genotype distribution	N	%
*GSTT1*0*	12	6.9
*GSTM1*0*	76	44.1
*GSTM*0 and GSTT*0*	11	6.4
GSTT+ and GSTM+	73	42.6



2. Associations between DNA variants and tumor clinicopathological features

- Carriers of combined *GSTT1* and *GSTM1* deletion had a significant correlation with the fact of cervical cancer progression (P = 0.026).
- The determined association cannot be used as a prognostic indicator for disease progression since logistic regression method could neither confirm nor deny the odds ratio for this relationship.
- No other significant relations with clinicopathological features of cervical cancer were found.

3. No significant relationships between GSTM1 and GSTT1 variants and patients´ OS and PFS in survival analysis



*Example of generated **Kaplan-Meier curves** for Overall survival and Progression free survival. A-B) Patients with GSTM1 null genotype had no increased risk for shorter PFS (P=0.592) and OS (P=0.568). P values are obtained by the Log-Rank test*

Genotype or alleles	Progression free survival			Overall survival		
	HR	95% CI	P	HR	95% CI	P
GSTM1 null genotype versus wild genotype	0.860	0.484-1.527	0.606	1.199	0.640-2.248	0.570
GSTT1 null genotype versus wild genotype	0.984	0.303-3.194	0.978	0.603	0.186-1.957	0.399
Both null genotype versus wild type	*	*	*	0.490	0.067-3.581	0.482

With Cox Regression model no prediction on survival of GSTM1 and GSTT1 null carriers compared to wild type carriers could be made since for all analyzed genetic groups sincd P values were statistically insignificant.
PFS for patients with double null genotypes could not be analyzed (*).
HR = Hazard Ratio, CI = Confidence interval

Conclusions

Carriers of combined *GSTT1* null and *GSTM1* null had a significant correlation with the fact of cervical cancer progression.

However, more detailed studies on larger cohort are recommended to confirm our findings. For more precise results gene-environmental and gene-gene interactions should be included in cervical cancer analysis.

Key words

GSTM1, GSTT1, Polymorphism, Cervical cancer