MMP-2 and MMP-8 polymorphism analysis and their prognostic value assessment in breast cancer patients

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Objective

Breast cancer (BC) is the most common women cancer and it accounts for approximately 25% of total cancer cases. It remains the leading cause of cancer mortality among women worldwide. Consequently, there is still an urgent need to improve our knowledge in BC biology what might lead to better treatment options.

Matrix metalloproteinases (MMP) are calcium-containing zinc-dependent endopeptidase. Their function is to degrade any type of extracellular matrix, what is important for tissue architecture and remodeling. Previous studies suggested that germline MMP polymorphisms are associated with inherited risk for tumor development and poor outcome in human breast cancer, however the results are inconclusive.

This study aimed to analyse the effect of MMP2 rs243665 and MMP8 rs112255395 polymorphisms on tumor pathomorphological characteristics and the cause of the disease.

Methods

- A retrospective study, involving 100 breast cancer patients, was conducted.
- The research protocol was approved by Kaunas Regional Biomedical Research Ethical Committee (protocol number BE-2-10 and BE-2-10/2014).
- Patient peripheral blood samples, obtained by clinicians in a time period 2014-2016, were used for the genomic DNA extraction.
- MMP2 -1306 C>T (rs243865) and MMP8 -799 C>T (rs11225395) promoter polymorphisms were analyzed with polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay (Figure 1 and 2).
- For association analysis patient clinical data were collected from medical records.
- The statistical analysis was performed using IBM “SPSS”.

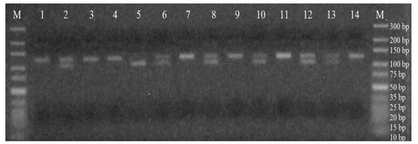

Figure 1. Agarose gel electrophoresis of RFLP products for MMP2 -1306C>T (rs243865) polymorphism analysis.
Lane M - DNA molecular marker GeneRuler Ultra Low Range DNA Ladder (Thermo Fisher Scientific Baltics, Lithuania); Lanes 1, 3, 4, 7, 9, 11 and 14: CC genotype; Lanes 2, 6, 8, 10, 12 and 13: CT genotype; Lane 5: TT genotype.

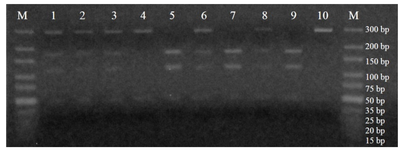

Figure 2. Agarose gel electrophoresis of RFLP products for MMP8 -799C>T (rs11225395) polymorphism analysis.
Lane M: DNA molecular marker GeneRuler Ultra Low Range DNA Ladder (Thermo Fisher Scientific Baltics, Lithuania); Lanes 1-3, 6 and 8: CT genotype; Lanes 5, 7 and 9: CC genotype; Lanes 4 and 10: TT genotype.

Results

- A group of young (30-40 years – 34%, 41-50 years – 66%) patients (N- 100) was involved in the study.
- The distribution of tumor pathomorphological parameter was as follows: estrogen positive (57%), progesterone positive (48%), HER2 overexpression - 22% of tumors. Approximately half of the studied BC patients (45%) had positive lymph nodes. The majority (71%) of the tumors were well to moderate differentiated (G1+G2) and most of them were classified as T1 (64%).
- The distribution of *MMP2* rs243865 and *MMP8* rs11225395 genotypes (Figure 3) was according to the Hardy-Weinberg equilibrium. The MAF of analyzed polymorphisms followed Hap-Map CEU, 1000 Genomes, ALFA and other world-wide conducted studies.
- In the association analysis it was determined that the carriers of C allele in *MMP8* rs11225395 polymorphism were less likely to develop tumors with positive PR when compared to the non-carriers in both univariate (p=0.011) and multivariate models (p=0.033).
- In the survival analysis it was demonstrated that the carriers of C allele in *MMP2* rs243865 polymorphism had lower probability of shorter PFS (Figure 4) that the non-carriers in both univariate (p=0.042) and multivariate models (p=0.033).

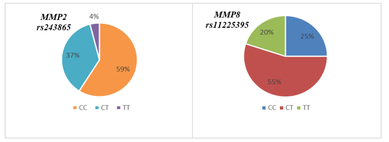

Figure 3. MMP2 rs243865 and MMP8 rs11225395 genotype distribution.

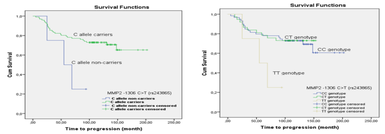

Figure 4. Kaplan-Meier curves for PFS according do different MMP2 -1306 C>T (rs243865) polymorphism genotypes and alleles.

Conclusions

Our data suggest that MMP2 rs243865 and MMP8 rs11225395 polymorphism are important for breast cancer phenotype and prognosis.

Key words

Breast cancer, SNPs, *MMP2, MMP8,* associations