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 cancer among women 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 endopeptidases. Their function is to degrade any type of extracellular matrix, what is important for tissue architecture and remodeling. Previous studies suggested that MMPs have a role in breast cancer development and poor outcome in human breast cancer, however the results are inconclusive.

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”.

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 (frequency) of the 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).

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.