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C-1589T AND G-1665A POLYMORPHISMS OF MATRIX METALLOPROTEIN-9 GENE PROMOTER INCREASED LEVEL OF MATRIX METALLOPROTEINASE-9 ENZYME AS A RISK FACTOR METASTATIC OF BREAST CANCER IN BALINESE TRIBE

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Background: Metastatic breast cancer is a cancer which grows and develops in other tissues or organs with the nature and type of cancer similar to its origin. The prevalence of metastatic breast cancer is quite high increase in the overall incidence rate of approximately 1.5% per year. Cancer metastatic is one of the factors increasing mortality and morbidity in patients with a low cure rate (30%). Evidence suggests that breast cancer is affected by genetics and non-genetics (epigenetic). Gene promoter polymorphisms of MMP-9 is one of the genetic factors that play a role in breast cancer metastatic. This research was conducted with the aim of whether the polymorphism C-1589T and G-1665A on MMP-9 gene promoter and high levels are a risk factor for breast cancer metastatic. **Methods**: This research has been done with cross sectional and case control study. Sixty six patient of breast cancer devided in two groups, thirty three with metastatic used as a samples and thirty three without metastatic used as a controls. PCR and sequencing techniques were used to presence of polymorphism and ELISA techniques used to determined levels of MMP-9 enzyme. **Results**: The research found C-1589T polymorphism (genotype-CT) and G-1665A (genotype-GA) and also with both genotype-CT and genotipe-GA (genotype-CT/GA). Genotypes were found to be associated with the occurrence of breast cancer by 51%. C-1589T polymorphism (genotype-CT) and G-1665A polymorphism (genotype-GA) increased levels of MMP-9 but were not risk factor for breast cancer metastatic (OR= 1.61; 95% CI= 0.41 to 6.34; p= 0.367) and (OR= 1.86; 95%CI= 0.62 to 5.61; p= 0.204). While polymorphism with both genotype (genotype-CT/GA) increasing levels of MMP-9 and indicated risk factor for breast cancer metastatic (OR= 8.62; CI95%= 0.99 to 74.57: p=0.027). **Conclusions**: Polymorphism with genotype-CT, genotype-GA and genotype-CT/GA found about 51% on breast cancer Balinese Tribe. Enzyme levels found to be higher in cases than in controls but not significantly different. Polymorphism with genotype-GA and genotype-CT increase levels of MMP-9 enzyme but not as risk factor for metastatic cancer while genotype-CT/GA increases levels of the enzyme MMP-9 and as a risk factor for breast cancer metastatic in Balinese Tribe.

Keywords: MMP-9 gene, polymorphism, levels of MMP-9, breast cancer, metastatic.

INTRODUCTION

Breast cancer (carcinoma mammae) is a cancer that occurs in breast tissue, is the most common cancer in female.[1] Breast cancer is a disease with the highest mortality rate in the world and number two cause of death after cardiovasculer disease.[2,3] Incidence of breast cancer continues to rise and more common in grade or advanced stage and metastatic conditions. Increasing the number of incidents also occurred in Indonesia, especially in Bali and more than 70% of breast cancer patients came to Sanglah General Hospital be on advanced stage and afer metastatic condition.[4,5]

Metastatic cancer is a process of migration of cancer cells into the surrounding tissue.[6,7] Cancer metastatic is a major cause of increased mortality and morbidity in patients with breast cancer. The prevalence of metastatic breast cancer is quite high about 1.5% per year and is one of the factors increasing mortality with a low cure rate of approximately 30%.[8,9]

Development and metastatic of breast cancer was multifactorial process due to an accumulation of changes in both genetic and non-genetic (epigenetic).[9,10] Involvement of a gene in pathogenesis of breast cancer has been widely linked. This group of genes are metaloproteinases (MMPs), especially MMP-9 gene.[9,10] Polymorphisms in the MMP-9 gene promoter can affect gene transcription and is

can help identify patients who have a high risk for the occurrence of metastases early so that it can be overcome. Given levels of MMP-9 enzyme were high and genotype CT/GA is a risk factor for metastatic, checks the levels of the enzyme MMP-9 and genotypes in patients diagnosed with cancer will be able to detect the risk of metastatic from the beginning so that metastatic can be anticipated.

Various studies of the MMP-9 gene polymorphism and its relation to the occurrence of metastatic breast cancer remains an interesting topic to be studied and researched. This is done because of genetic factors in particular C-1589T and G-1665A polymorphism on MMP-9 gene promoter has been shown to be associated with the occurrence of breast cancer metastatic. Thus the role of genetic factors in reducing the risk of metastatic, especially those that proved to be a risk factor can be early detected and well anticipated.

Three variants of polymorphisms were found in this study, polymorphism with genotype-CT/GA or the haplotype CT/GA increases MMP-9 enzyme levels are highest and are risk factors for breast cancer metastatic compared with genotype-CT and genotype-GA (OR = 8.615; 95% CI 0.99 to 74.57: p = 0.027). Results of this study prove that the polymorphism analysis is very important to be done, especially in the promoter region of genes as associated with gene expression to transcription and translation in the process of protein synthesis and also to the activity of the enzyme.[19,12]

CONCLUSIONS

Polymorphism with genotype-CT, genotype-GA and genotype-CT/GA found 51% in breast cancer patients Balinese Tribe. Levels of MMP-9 enzyme found to be higher in cases than in controls but not significantly different.

Polymorphism genotype-CT and genotype-GA increase levels of MMP-9 enzyme but is not as risk factor for cancer metastatic while polymorphism with genotype CT/GA increase levels of MMP-9 enzyme and as a risk factor for breast cancer metastatic Balinese Tribe.

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