**Genetic and epigenetic characterization of the *BRCA1* gene in Brazilian women at-risk for hereditary breast cancer.**

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Breast cancer (BC) constitutes the leading cause of cancer mortality among women, and about 5-10% of cases are hereditary. The identification of hereditary cases is important because affected individuals are vital cumulative risk much higher than the population for the development of various cancers. A family history of cancer is a classic risk factor. However other factors, such as the histopathological characteristics of *BRCA*-associated tumors, significantly impact the identification of families with hereditary BC. So our objective was to characterize women at-risk for hereditary BC regarding to the clinical and molecular characteristics (mutation and methylation in the *BRCA1* gene) and correlate the gene expression levels with histopathological and clinical data, prognosis, survival and family history. The study included 72 women (patients), who were grouped according to the mutational status of *BRCA1*: 19 in *BRCA1*-pathogenic group, 16 in *BRCA1*-VUS group and 37 in *BRCA1*-WT group. Most patients had invasive ductal carcinoma. The average age at diagnosis was 42.0 years (SD = 7.7) for women *BRCA1*-pathogenic group, 37.2 years (SD = 9.1) for those with VUS and 38.8 years (SD = 10.5) for women *BRCA1*-WT group. Most tumors of women with mutated *BRCA1* was triple negative (65.0%) and had histologic grade III (57.9%), unlike the other two groups where the predominant histological grade II and luminal B. For overall survival and event-free, we found no difference between the three groups analyzed. Additionally, through the analysis of family history we noted that the women of *BRCA1*-pathogenic group had more cases of breast cancer in the family as well as a higher percentage of cases younger than 50 years. As regards the methylation profile, no patient with a pathogenic mutation in *BRCA1* showed hypermethylation, and this phenomenon (hypermethylation) was observed in only two patients (patients from *BRCA1*-VUS and the *BRCA1*-WT groups). Thus, there were no cases of co-ocurrence of germline mutation and hypermethylation of the *BRCA1* gene. Regarding the profile of gene expression, most of the patients of all three groups had lower levels of *BRCA1* mRNA in tumor tissue, thereby indicating the loss/decrease of gene function in methylated and in mutated cases, and also in cases with absence of these events suggesting that other mechanisms could be working on the silencing of this gene. In summary, our findings suggest that methylation in the *BRCA1* gene is not the "second event" for the development of BC in patients with germline mutation in *BRCA1*. Furthermore, since a reduction in the *BRCA1* mRNA levels was observed for the three groups, it is suggested that other mechanisms may be involved or still that methylation analysis spanning the whole promoter region of the *BRCA1* gene or the body gene should be considered.