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Investigation of global methylation and promoter methylation of two tumor suppressor genes in peripheral blood for breast cancer early detection

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Breast cancer (BC) is the most common cancer in women around the world, and it is also the primary cause of cancer mortality among women. Early detection of breast cancer makes a contribution to decrease the mortality rate and improve prognosis for the patients. Nevertheless, mammography as an early detection method has its limitations especially in young women, Asian, women, who undergo a hormone replacement therapy, and/or women have high density of breasts. Thus, alternative approaches for screening and diagnosis of breast cancer are needed. Numerous biomarkers have been used to evaluate the outcome of breast cancer, but there is lack of some markers for breast cancer early detection and risk prediction. Blood cell DNA methylation could be a promising biomarker for early detection of breast cancer.

Here, a case-control study was carried out to investigate alterations of global DNA methylation status, LINE1 and Alu, and promoter methylation changes of two tumor suppressor genes (RASSF1A and ATM) in peripheral blood DNA from breast cancer patients and healthy controls. The aim was to find some potential biomarkers for breast cancer risk. The methylation levels of LINE1, Alu, RASSF1A and ATM were measured in 229 sporadic cases and 151 controls by MassARRAYEpityper assay. Results showed that the mean methylation level of investigated CpG sites of LINE1 in peripheral blood from breast cancer patients was lower than that in controls (P = 8.78E-06) and especially for LINE1_CpG_1 (P = 3.64E-10). ROC curve analysis of LINE1_CpG_1 methylation and LINE1 mean methylation was used to estimate the potential clinical utility of LINE1 methylation, AUC was 0.73 (95% CI: 0.68-0.79) for LINE1_CpG1 and 0.68 (95%CI 0.62-0.74) for LINE1 mean methylation, respectively. In addition, the highest increased risk was observed in the lowest quartile of LINE1_CpG_1 methylation and of LINE1 mean methylation (OR = 38.47 and 5.94; 95% CI: 8.77-168.64 and 2.94-11.98; P for trend = 1.42E-07 and 1.33E-05 respectively). For Alu, a

significant hypomethylation of Alu_CpG_13 and Alu_CpG_14 in peripheral blood of breast cancer cases compared to controls was observed (P = 0.002 and 0.006, respectively). In the combined analysis, a panel of 10 CpG sites within LINE1 and Alu resulted in an AUC of 0.77 (95% CI: 0.72-0.83). The investigation of RASSF1A and ATM promotor methylation showed no significant differences of methylation levels in peripheral blood DNA between BC cases and controls.

In summary, the here presented work indicate that the decreased methylation level of certain CpG sites in LINE1 and Alu elements in peripheral blood cell DNA are associated with BC. These markers might contribute to a blood-based, molecular multi-marker panel for breast cancer early detection. Further multicentric studies with large sample sizes and prospective studies with highly standardized blood sample processing, are required to validate the here investigated markers and generally methylation changes in blood cell DNA between sporadic and/or familial BC and healthy controls.