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**RASSF1A methylation is predictive of poor prognosis in female breast cancer in a background of overall low methylation frequency.**

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**Abstract**

Breast cancer (BC) is the most common cancer worldwide. The Kingdom of Saudi Arabia is no exception, with ever increasing incidence rates. An interesting feature of this disease is the relatively young age of the affected women. The average age in the present cohort of 100 sporadic cases of invasive ductal carcinomas was 45 years, with a median of 46 years (range between 19-81 years). In an effort to understand the molecular signature of BC in the Saudi population, we undertook this study to profile the methylation events in a series of key genes including Ras association (RalGDS/AF-6) domain family member 1 isoform a (RASSF1A), hypermethylated in cancer 1 (HIC1), cyclin-dependent kinase inhibitor 2A (CDKN2A), retinoic acid receptor beta (RARβ), estrogen receptor 1 (ESR1), progesterone receptor (PGR), paired-like homeodomain 2 (PITX2), secreted frizzled-related protein 1 (SFRP1), myogenic differentiation 1 (MYOD1), and slit homolog 2 (SLIT2), using MethyLight analysis in archival tumour samples. Interestingly, the overall methylation levels were low in this cohort, with only 84% of the cases displaying methylation in one or more of the analysed genes. The frequency of RASSF1A methylation was the highest (65%), while there was almost complete absence of methylation of the ESR1 and the CDH1 genes (1% and 3%, respectively). Several statistically significant correlations were identified between specific methylation events and clinical parameters which gained more significance when analysis was limited to the estrogen receptor positive samples. Although there was no significant correlations between any methylation event and disease-specific survival, methylation of MYOD1 or RASSF1A was associated with lower disease-free survival and increased chance of disease recurrence. Furthermore, multivariate (Cox) regression analysis identified RASSF1A as an independent predictor of poor prognosis in terms of disease-free survival in this cohort. Our findings provide further evidence on the usefulness of RASSF1A methylation status as an informative prognostic biomarker in BC in a Saudi population