DNA hypermethylation of PITX2 is a marker of poor prognosis in untreated lymph node-negative hormone receptor-positive breast cancer patients.

BACKGROUND: In this study, we evaluated if PITX2 DNA methylation is a marker for disease recurrence in lymph node-negative (LNN), steroid hormone receptor-positive (HR+) breast cancer patients. In addition, we studied the association between PITX2 DNA methylation and PITX2 gene expression. PATIENTS AND METHODS: PITX2 DNA-methylation was measured in tumor tissue from 412 LNN/HR+ breast cancer patients who had not received any adjuvant systemic treatment. In addition, PITX2 DNA-methylation and mRNA expression was evaluated in 32 breast cancer cell lines. RESULTS: In univariate Cox regression analysis, DNA-methylation of PITX2 as a continuous variable was associated with early distant metastasis (HR = 1.71; P < 0.01) and poor overall survival (HR = 1.71; P < 0.01). In multivariate analysis together with the established prognostic factors age, tumor size and tumor grade, and steroid hormone receptor levels, both associations retained their significance (for MFS, HR = 1.74; P < 0.01; for OS, HR = 1.46; P = 0.02). In the breast cancer cell lines, PITX2 DNA methylation was inversely association with PITX2A and PITX2B mRNA expression (P < 0.01).
CONCLUSIONS: Hypermethylation of PITX2 is, in cell lines, negatively associated with PITX2 mRNA expression and, in clinical specimens, positively associated with breast cancer disease progression.