Combined PTEN and p27kip1 protein expression patterns are associated with obesity and prognosis in endometrial carcinomas

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Author(s) Dellas, Athanassios; Jundt, Gernot; Sartorius, Gideon; Schneider, Mischa; Moch, Holger
Author(s) at UniBasel Jundt, Gernot ; Dellas, Athanassios ;
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PURPOSE: Phosphatase and tensin homologue deleted from chromosome 10 (PTEN) and p27(kip1) proteins are key players of the Akt pathway, which is nutritionally regulated by insulin receptor signaling and influenced by estrogens. In this study, the prognostic relevance of the PTEN/p27(kip1) protein expression in endometrial carcinoma in relationship to the body mass index (BMI) was determined. EXPERIMENTAL DESIGN: BMI and prognosis of 452 surgically treated patients with endometrial carcinoma were correlated with histologic subtype, International Federation of Gynecology and Obstetrics (FIGO) stage, and differentiation grade. The expression of PTEN and p27(kip1) was examined in 257 tumors by immunohistochemistry using a tissue microarray approach. RESULTS: Lack of PTEN was observed in 136 of 257 (53%) tumors and absence of p27(kip1) expression was observed in 106 of 225 (47%) tumors. Absence of both proteins was significantly associated with well-differentiated tumors [PTEN ($P > 0.02$) and p27(kip1) ($P > 0.009$)]. Differentiation grade, tumor stage, and histologic type were independent of an increased BMI. Importantly, tumors of obese women expressed significantly less PTEN ($P > 0.008$) and less p27(kip1) ($P > 0.01$) than tumors from nonobese patients. Combined absence of both PTEN and p27(kip1) expression characterized a group of 75 (32%) tumors with favorable clinical outcome, particularly in the FIGO stages I and II ($P = 0.003$) of obese patients. Cox regression analysis revealed that PTEN/p27(kip1) phenotype, FIGO stage, and histologic grade were independent predictors of prognosis in endometrioid endometrial carcinoma. CONCLUSIONS: Inactivation of PTEN/p27(kip1) proteins is a specific feature in the progression of endometrial carcinoma in obese patients. The phenotype of the combined loss of PTEN/p27(kip1) protein expression in obese patients is associated with a significantly better prognosis in endometrioid endometrial carcinoma.

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