Differential Expression Patterns of PTEN in Cyclic, Hyperplastic and Malignant Endometrium: Its Relation with ER, PR and Clinicopathological Parameters

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ABSTRACT

PTEN is a tumor suppressor gene, which is frequently mutated and involved in the control of cell proliferation, differentiation, and apoptosis in a variety of human tumors including endometrium. We hypothesized that PTEN expression in endometrium is variable throughout the menstrual cycle as well as different endometrial lesions, and that steroid hormones regulate PTEN expression because PTEN is critical in many steroid-sensitive tissues such as endometrium.

Aim of Work: In this study, we aimed to assess the relationships between PTEN expression and estrogen (ER), progesterone receptors (PR) in normal endometrium, hyperplasia and endometrial carcinoma.

We also evaluated the relationship between PTEN expression and clinicopathologic parameters including tumor grade, stage and myometrial invasion in endometrial carcinoma.

Methods: Specimens included 12 cyclical endometrium, 12 cases endometrial hyperplasia without atypia, 8 cases atypical endometrial hyperplasia and 35 endometrial carcinoma specimens. Immunohistochemical staining for PTEN protein, ER and PR was performed with the Streptavidin-biotin method on formalin-fixed and paraffin-embedded tissue samples. PTEN, ER and PR expression was represented as the staining score.

Results: Immunohistochemistry showed that PTEN, ER and PR were positive for nuclei of cells. The PTEN staining score of normal endometrium was higher in the proliferative phase than in the secretory phase. The PTEN scores in atypical hyperplasia and endometrial carcinoma were significantly lowered than those for cyclic and hyperplasia without atypia. In endometrial carcinoma, PTEN expression was significantly correlated with histological grade while no significant associations with either stage or myometrial invasion were seen. Significant correlations were detected between PTEN and PR in EC cases and between PR and ER in all lesions, while no correlation was seen between ER and PTEN in different lesions.

Conclusions: PTEN expression has been changes throughout the menstrual cycle. We suggest that PTEN is involved in the early stages of endometrial carcinogenesis. In endometrial carcinomas, loss of PTEN expression is involved in tumor cell differentiation.

Key Words: PTEN – Cyclic – Hyperplastic – Malignant endometrium – Estrogen receptor – Progesterone Receptor

INTRODUCTION

PTEN (PHOSPHATASE and TENSIN homolog deleted on chromosome 10) is a tumor suppressor gene with three independent groups [1,2]. Its name derives from its preserved tyrosine phosphatase domain and its sequence homology with the matrix protein with a 55-kD gene product and protein composed of 403 amino acids. PTEN is a dual-specificity phosphatase with a sequence similar to that of the cytoskeletal protein tensin [3-6].
A strong correlation was found between its phosphatase and tumor suppressor activity that has been demonstrated previously in many advanced cancers in vitro [7-9]. PTEN protein functions as a lipid phosphatase that helps to modulate cell signal transduction pathways by acting on phospholipid phosphatidylinositol-(3,4,5)-triphosphate (PIP3), a second messenger produced after growth factors bind to cell surface membrane receptors. Decreased PTEN activity or loss-of-function lead to constitutive activation of multiple signaling pathways, including the PI3K/Akt pathway, which in turn affects cell proliferation, apoptosis and migration [10,11].

Mutation of PTEN is a common event in a wide range of human tumors such as glioblastoma [2,12], ovary [13], prostate [14], breast [15], thyroid [16], and endometrium [17-19]. Moreover, autosomal dominant inherited hamartoma syndrome associated with increased cancer risks such as Cowden disease is due also to germline mutations in PTEN gene [20]. In endometrial carcinoma (EC), PTEN mutations were detected in 45.7-83% of endometrial adenocarcinoma; this is the highest known frequency of PTEN mutations in any primary tumor analyzed [19,21,22]. In this tumor, PTEN mutations were confined to the endometrioid subtype, which accounts for nearly 80-90% of endometrial cancers. Up to 25-83% of EC, reveal altered PTEN expression [21,23,24].

PTEN mutations are involved early in endometrial carcinogenesis, in endometrial hyperplasias with or without atypia, which are precursors of endometrioid carcinoma, in which its mutation has been detected in 19-55% [17,19,22]. PTEN expression in both mRNA and protein level throughout the menstrual cycle, showing cyclic-related changes has been reported [18].

ER and PR are ligand-dependent transcriptional factors belonging to the nuclear steroid receptor superfamily [25]. They have an important role in normal endometrial function, pathogenesis, the expression and relationship of the two distinct ER's and PR’s could be of essential clinical implications [26,27]. In a previous study investigated PTEN levels and its phosphorylation in endometrial cells in response to sex steroids [28], showed that phosphorylation of the PTEN tail inhibits PTEN activity and decreases its degradation. Others reported that the regulation of PTEN expression by ovarian steroids might help to protect the balance between proliferative and antiproliferative actions in normal endometrium [29].

In this study, we hypothesized that PTEN expression in human endometrium is variable throughout the menstrual cycle and among different endometrial lesions and that, ovarian steroid hormones (estrogen and progesterone) regulate PTEN expression. We evaluated PTEN immunohistochemical expression in normal endometrium, endometrial hyperplasia and endometrioid adenocarcinoma as well as, the correlation of PTEN expression with clinicopathological parameters. We further investigated the association of PTEN, ER and PR in different lesions as well as normal endometrium.

**MATERIAL AND METHODS**

**Tissue specimens:**

Formalin-fixed and paraffin-embedded specimens were collected and prepared for this study from El-Minia University Hospital in collaboration with the cancer unit in the Obstetrics and Gynaecology department, El-Minia University. Specimens included 12 cyclical endometria (six cases were proliferative and six cases were secretory), 12 cases endometrial hyperplasia without atypia (six cases were simple and six cases were complex), eight cases were atypical endometrial hyperplasia and 35 were endometrial carcinoma (EC) specimens. All EC patients had undergone surgical intervention according to the protocol in the unit total (the minim surgical intervention were total abdominal hysterectomy and bilateral salpingio-ophrectomy). Cyclical endometrium and hyperplasia samples were obtained either by curettage or biopsy specimens. Endometrial dating was done according to Zaino’s criteria [30]. Hyperplasia specimens were evaluated according to WHO classification [31]. Regarding EC cases, grading and staging were assessed according to the International Federation of Gynecology and Obstetrics criteria [32,33].

**Immunohistochemistry:**

Four-micron thick sections were transferred to adhesive slides from representative formalin-fixed, paraffin-embedded blocks. The sections were deparaffinized in xylene and dehydrated through a series of graded alcohols. Antigen
retrieval was performed in a microwave oven for 10 minutes. To block endogenous peroxidase activity, the sections were incubated with 0.3% hydrogen peroxide in methanol for 30 minutes after cooling to room temperature. The monoclonal antibodies for PTEN (clone 28H6 dilution 1/100, Lab Vision corporation), ER (clone 1D5, DAKO Cytomation), PR (clone 1A6, DAKO Cytomation) were added. A biotinylated secondary antibody was applied to sections for 30 minutes at room temperature. After incubation, the reaction product was visualized using diaminobenzidine. Finally, the sections were counterstained with hematoxylin.

Positive and negative control:
Negative control sections were treated with phosphate-buffered saline (PBS) instead of primary antibody. Endometrial stromal cells sections were used as internal positive control for PTEN staining while sections of human breast cancer were used as positive control for ER and PR.

Statistical analysis:
Raw data were used to determine means, standard deviations and ranges. Nonparametric ANOVA, Kruskal-Wallis test was used to compare means of expression in different groups followed by post test, Dunn’s multiple comparisons test to compare means between two groups. Correlation between markers in different lesions was conducted with Spearman’s rank correlation test. Kruskal Wallis test was used to examine the correlation of PTEN staining scores in relation to tumor grade, stage and myometrial invasion. \( p \)-value of \(<0.05\) was considered statistically.

Statistical analysis was conducted using GraphPad InStat program version 3.

Scoring system:
Immunohistochemical results were evaluated according to Kapucuoglu et al. [22]. Immunoreactivity was graded semiquantitatively by considering the percentage and intensity of the staining overall section. A histologic score was obtained from each sample, ranging from 0 (no immunoreaction) to 300 (maximum immunoreactivity). The score was obtained by applying the following formula: 
\[
H_{\text{score}} = 1x \text{ (% light staining)} + 2x \text{ (% moderate staining)} + 3x \text{ (% strong staining)}.
\]

RESULTS

Immunohistochemical results:
Positive expression rates, Mean values and standard deviations of H scores for PTEN, ER and PR in different lesions are listed in (Table 1).

PTEN immunohistochemistry:
PTEN expression was predominantly nuclear with positive expression in endometrial glandular and stromal cells (Fig. 1a-f). On studying the PTEN expression in different lesions, we found decreased expression in AH and EC cases compared to CE and EH as shown in (Table 1). As regard cyclic endometrium, we found, in proliferative phase (PP), PTEN, mean±standard deviation 155.83±56.96, while in secretory phase (SP), PTEN, 101.67±29.27, that was lower than in proliferative phase.

Regarding its expression in different lesions, statistically significant differences were seen between CE and EC (\( p<0.05\)) and between AH, CE and EH (\( p<0.01,\) \( p<0.001\) respectively). As regard cyclic endometrium, significant differences were found between PP and EC (\( p<0.05\)). No significant differences were detected between PTEN expression in PP and other groups or between SP and any of examine groups. In addition, no significant difference was noticed between PTEN expression in PP and SP.

ER immunohistochemistry:
ER positivity was noted in the nucleus of glandular and endometrial stromal cells. Positive expression was noticed in all sections of CE, EH and AH while decreased in EC with an expression rate of 88.6% (Table 1). For cyclic endometrium, we found, in PP and SP the mean±standard deviation was 269.17±26.54, 145.00±70.64 respectively. Regarding its expression in different lesions, statistically significant differences were identified between EC and CE, EH (\( p<0.001\) for both). Regarding cyclic endometrium, a statistically significant difference between PP and EC was identified (\( p<0.001\)).

PR immunohistochemistry:
PR expression was seen in the nucleus of glandular and endometrial stromal cells. The expression rate in CE, EH and AH was 100% of cases while decrease in EC (94.3%) (Table 1). For cyclic endometrium, we found, in PP and SP the mean ± standard deviation was
255.83±33.23, 165.83±58.69 respectively. Regarding its expression in different lesions, statistically significant differences between EC and CE, EH (p<0.01 for both). There were no statistically significant differences between EH, AH and CE. For cyclic endometrium a statistically significant differences between PP and EC (p<0.001).

Table (1): Positive expression rates, mean values and standard deviations of H scores for PTEN, ER and PR in different lesions.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Lesion</th>
<th>No</th>
<th>% +ve</th>
<th>Mean ± Std. Deviation</th>
<th>95% CI LB</th>
<th>95% CI UB</th>
<th>Min</th>
<th>Max</th>
<th>p-value among four groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN*</td>
<td>CE</td>
<td>12</td>
<td>100</td>
<td>128.75±51.61</td>
<td>95.95</td>
<td>161.54</td>
<td>70</td>
<td>225</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>EH</td>
<td>12</td>
<td>100</td>
<td>165.00±61.38</td>
<td>125.99</td>
<td>204.0</td>
<td>90</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AH</td>
<td>8</td>
<td>75</td>
<td>66.25±44.38</td>
<td>29.14</td>
<td>103.35</td>
<td>0</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC</td>
<td>35</td>
<td>51.4</td>
<td>51.57±53.69</td>
<td>33.12</td>
<td>70.0</td>
<td>0</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>ER**</td>
<td>CE</td>
<td>12</td>
<td>100</td>
<td>207.08±82.41</td>
<td>154.71</td>
<td>259.45</td>
<td>80</td>
<td>300</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>EH</td>
<td>12</td>
<td>100</td>
<td>220.41±51.54</td>
<td>187.66</td>
<td>253.16</td>
<td>150</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AH</td>
<td>8</td>
<td>100</td>
<td>157.50±81.37</td>
<td>89.47</td>
<td>225.16</td>
<td>50</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC</td>
<td>35</td>
<td>88.6</td>
<td>89.42±63.79</td>
<td>67.51</td>
<td>111.34</td>
<td>0</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>PR***</td>
<td>CE</td>
<td>12</td>
<td>100</td>
<td>210.83±65.39</td>
<td>169.28</td>
<td>252.38</td>
<td>70</td>
<td>300</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>EH</td>
<td>12</td>
<td>100</td>
<td>217.08±52.67</td>
<td>183.61</td>
<td>250.55</td>
<td>140</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AH</td>
<td>8</td>
<td>100</td>
<td>162.50±85.48</td>
<td>91.03</td>
<td>233.96</td>
<td>50</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC</td>
<td>35</td>
<td>94.3</td>
<td>115.14±70.26</td>
<td>90.0</td>
<td>139.28</td>
<td>0</td>
<td>230</td>
<td></td>
</tr>
</tbody>
</table>

Test of significance: Kruskal-Wallis Test with post test
* CE Vs EC, p<0.05; EH Vs AH, p>0.01; EH Vs EC, p>0.001; CE Vs EH, p>0.05; CE Vs AH, p>0.05; AH Vs EC, p>0.05.
** CE Vs EC, p<0.001; EH Vs EC, p<0.001; CE Vs EH, p>0.05; EC Vs AH, p>0.05; EH Vs AH, p>0.05; AH Vs EC, p>0.05.
***CE Vs EC, p<0.01; EH Vs EC, p<0.01, CE Vs EH, p>0.05; CE Vs AH, p>0.05; EH Vs AH, p>0.05; AH Vs EC, p>0.05.

Correlations between immunohistochemical markers in different lesions:

Significant positive correlations were noted between PTEN/PR (r=0.589, p=0.04) in cyclic endometrium. Similarly, a significant positive correlations were noted between PTEN/PR (r=0.498, p=0.002) in EC.

No significant correlations were noted between PTEN/ER in different lesions including CE (r=0.376, p=0.229), EH (r=0.084, p=0.795), AH (r=0.442, p=0.298) & EC (r=0.264, p=0.125). In addition, no significant correlations were found between PTEN/PR in EH and AH (r=0.084, p=0.795, r=0.422, p=0.298 respectively). We also noticed significant positive correlations between ER and PR expression in different lesions, CE (r=0.768, p=0.0004), EH (r=0.975, p=0.001), AH (r=0.089, p=0.003) & in EC (r=0.636, p<0.001).

Associations between PTEN expression scores and clinicopathological data in EC:

Associations between clinicopathological data and PTEN expression were summarized in (Table 2). A significant association between decreased PTEN expression and tumor grade (p= 0.01) was detected. No significant associations were noticed between PTEN expression and either stage or myometrial invasion.

Table (2): Associations between PTEN expression scores and clinicopathological data in EC.

<table>
<thead>
<tr>
<th>Clinicopathological parameter</th>
<th>No. of cases</th>
<th>Mean ± Std. Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1*</td>
<td>9</td>
<td>87.77±51.90</td>
<td></td>
</tr>
<tr>
<td>GII</td>
<td>13</td>
<td>53.07±54.52</td>
<td>0.01</td>
</tr>
<tr>
<td>GIII*</td>
<td>13</td>
<td>25.00±40.62</td>
<td></td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>77.22±51.42</td>
<td>0.475</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>43.63±50.25</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>43.33±54.31</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>40.00±63.24</td>
<td></td>
</tr>
<tr>
<td>MI:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>67.85±55.6</td>
<td></td>
</tr>
<tr>
<td>&lt;1/2</td>
<td>20</td>
<td>57.00±53.91</td>
<td>0.27</td>
</tr>
<tr>
<td>&gt;1/2</td>
<td>8</td>
<td>23.75±47.79</td>
<td></td>
</tr>
</tbody>
</table>

Test of significance: Kruskal Wallis test
p-value <0.05 are considered significant
* G1 Vs G3, p<0.05
Fig. (1A-F): PTEN protein expression in different endometrial lesion.

Fig. (1A): PTEN expression in the proliferative phase of normal endometrium. Showing almost all nuclei of glandular cells and stroma show the immunoreactions (DAB-hematoxylin counterstain X200).

Fig. (1B): PTEN expression in the secretory phase, showing positive nuclei in the glandular and stromal cells (DAB-hematoxylin counterstain X400).

Fig. (1C): PTEN expression in simple endometrial hyperplasia. Almost all nuclei of glandular cells and stroma show the immunoreactions (DAB-hematoxylin counterstain X200).

Fig. (1D): PTEN expression in atypical complex endometrial hyperplasia, showing PTEN expression pattern is heterogeneous, in which PTEN-negative hyperplastic cells are adjacent to a PTEN-positive hyperplastic cells (DAB-hematoxylin counterstain X400).

Fig. (1E): PTEN expression in endometrial carcinoma showing reduced number of positive cells (DAB-hematoxylin counterstain X400).

Fig. (1F): PTEN expression in endometrial carcinoma showing strong-positive immunoreactions (DAB-hematoxylin counterstain X400).
DISCUSSION

PTEN is a tumor suppressor gene that plays a significant role in inducing cell cycle arrest and programming apoptosis, and in cell physiology, including the regulation of cell adhesion, migration, and differentiation [34]. Nuclear PTEN localization has been shown by numerous studies [35-37]. It is the most frequently altered gene in endometrial carcinoma and its precursor lesion hyperplasia [23,24].

Normal endometrium is hormonally regulated in a cyclic manner and undergoes highly dynamic changes throughout the menstrual cycle mediated and controlled by estrogen and progesterone [38]. It was reported that endometrial PTEN expression changes throughout the menstrual cycle [18,29]. Consistent with the data of those studies, our results suggest PTEN expression difference in cyclic endometrium that is under the control of cyclic effect of estrogen and progesterone. We noticed a higher, although not significant PTEN staining score in the proliferative endometrium than in the secretory endometrium. Other studies reported that all glandular and stromal endometrial cells in the proliferative phase were positive for PTEN, and that PTEN expression was decreased or absent in the secretory phase [18,39,40]. This suggests that PTEN protein may be induced in the proliferative phase as a negative feedback response to the stimulatory effect of estrogen on proliferation, and may be decreased in the secretory phase due to antagonism of estrogen's action by progesterone [18,19,39].

In the present study, we found that PTEN expression obviously decreased in both AH and EC compared to normal proliferative endometrium, and such decrease was statistically significant between PP and EC. Similar finding was reported by a previous study [41].

It was reported that loss of PTEN expression ranged from 19-55% in hyperplasia [17,19,22]. In the present study, PTEN immunoreactivity was noticed in all cases of EH, there was no complete loss of expression as in AH. We found a significantly lower PTEN scores in AH compared to EH. A finding that agrees with Kapucuoglu, et al. [22], and incompatible with Kimura, et al. [40], who showed no significant differences among subtype of hyperplasia. It has been reported that, in studying a group of patients with subsequent endometrial carcinoma and others without, the loss of PTEN protein expression was 55% in patients with subsequent endometrial carcinoma, while the frequency of absent protein expression in patients without subsequent cancer was 8%. Carcinoma developed in 44% in atypical complex hyperplasia, 10% in complex hyperplasia, and 0% in simple hyperplasia [42]. In our study, among cases of AH, we found loss of PTEN protein expression in 25% cases, in which the subsequent or coexisting carcinoma risk was high class. This result was comparable to An et al. [21], who detected no PTEN immunoreactivity in 30% of hyperplasias accompanying endometrial carcinomas. As follow-up data were not available in our study, it could not be clarified whether carcinoma can develop in those totally PTEN-negative cases of AH.

In present study, we detected a significantly higher PTEN expression in EH than in EC, while no significant difference was seen between AH and EC. This results are similar to results reported by Kapucuoga, et al. [22], suggesting that AH is the precursor of EC [43]. Common histopathologic criteria between EC and AH are present [44,45], that morphological finding is comparable to our finding that no statistically significant differences in PTEN expression levels between AH and EC were found. Previous molecular studies have found that 34-83% of all tumors and 55% of endometrial intraepithelial hyperplasias, which are regarded as precancer lesions, harbor point mutations or deletions within the PTEN gene, indicating that PTEN inactivation is an early event in endometrial carcinogenesis [18,23,46].

In our study, loss of PTEN immunoreactivity was 48.6% in EC and comparable to reported data that showed 45.7-83% of endometrial carcinomas [19,21,22] indicating the high rate of PTEN inactivation in EC, which was shown in prior DNA studies [47].

As regard grade of EC, a significant negative correlation between PTEN expression and grade was identified particularly between grade 1 and grade 3 tumors. Similar results reported a significant negative correlation between PTEN expression and FIGO grade [22]. Konopka, et al. [48], reported that, in well-differentiated endometrial carcinomas G1, the frequency of PTEN mutations was only half of that found in
less differentiated carcinomas G2 suggesting a higher PTEN expression in well differentiated tumors compared to less differentiated tumors. As suggested by Konopka, et al. [48], defects in PTEN gene may be associated with loss of the ability of endometrial cells to differentiate and thus increasing its malignancy. On the contrary, Kimura, et al. [40], reported higher PTEN expression in grade 3 tumors than in grade 1 and 2 tumors. They suggested that PTEN protein might have been induced to inhibit the aggressive growth of poorly differentiated carcinomas, whereas in well-differentiated cancers, PTEN might have been expressed at a low level. In the series of An, et al. [21], reported slightly more altered PTEN expressions in grade 1 and 2 endometrioid carcinomas compared to grade 3, but this difference was not statistically significant. In the present series, we found no association between PTEN protein expressions and either tumor stage or MI, a finding that was also reported by previous studies [21,22,40].

There have been several studies measuring ER and PR in the human endometrium. Our results confirm the cyclical variations of ER and PR as described by several authors [26,27,49]. We found that ER levels are maximal in the proliferative phase and decline in the secretory phase of the cycle, a finding that was consistent with Fujishita, et al. [50]. The ER expression might play an important role in normal endometrial function and pathogenesis and the expression and relationship of these steroid receptors could be of essential clinical value [48]. We also noticed significant positive correlations between ER and PR expression in different lesions except for secretory endometrium. Fukuda, et al. [51], also reported a significant correlation between ER and PR that is similar to our finding.

A positive correlation was detected between ER and PTEN expression only in simple hyperplasia and this may be related to its role to control increased proliferative activity due to increased estrogen expression in simple hyperplasia, PTEN expression is increased as an active control mechanism [22]. Consistent with our finding, there was no association between PTEN and ER expression in hyperplasia [22].

We also detected no correlation between PTEN expression and ER activity in endometrial carcinomas. This is consistent with the findings of Salvesen, et al. [52], and Kapucuoglu et al. [22] who reported lack of significant association between PTEN and ER in EH and EC and suggested a lack in active control mechanisms that control increased proliferative activity due to increased estrogen expression in different lesions.

We found a significant correlation between PTEN and PR in EC. Low PTEN was reported in tumors with high ER and PR expression levels and In vitro studies suggest that in endometrial cells PTEN expression is regulated by progesterone but not estrogen in a long-term manner [40].

In conclusion, endometrial PTEN expression rates vary throughout the menstrual cycle. Statistically significant differences in PTEN protein expression between EH and both of AH and EC were detected, while no significant differences were noticed between AH and EC. As AH is considered the precursor of endometrioid carcinoma, one might suggest that altered PTEN expression is implicated in the early stages of endometrial carcinogenesis. The significant negative correlation between PTEN expression and grade reported by the current study might suggest that PTEN is involved in tumor cell differentiation.

REFERENCES


