DOI: 10.7860/JCDR/2025/75346.20482

Review Article

Pathology Section

# Loss of PTEN Immunoexpression in Endometrial Carcinoma: A Narrative Review

GARIMA CHANDRAKAR[1], ARVIND BHAKE[2]




## ABSTRACT

Endometrial carcinoma is one of the important health issues addressed globally. Therefore, understanding the molecular pathogenesis of endometrial carcinoma for the purpose of prognostic and predictive markers remains in the centre of research. It has been reported in recently published literature that loss of Phosphatase and Tensin Homolog (PTEN) expression, a tumour suppressor gene, is one of the key events in the pathogenesis of endometrial carcinoma. This review aims to study the data for loss of PTEN expression in literature. Based on the inclusion and exclusion criteria, eight studies were finally included in the review. Comparative statistics of various studies showed that loss of PTEN expression is a key molecular event in endometrial carcinoma. The detection of lost PTEN expression could help in knowing the progressive nature of Atypical Endometrial Hyperplasia (AEH) and in distinguishing AEH from endometrial carcinoma. This will facilitate the choice of targeted therapy.


**Keywords:** Atypical endometrial hyperplasia, Immunohistochemistry, Tumour suppressor gene

## INTRODUCTION

Endometrial carcinoma is one of the most common invasive cancers of female genital tract which counts for 7% of all the invasive cancers, with an incidence of 2.3 per lakh women in India [1,2]. The incidence of endometrial carcinoma is increasing by every passing year as the urbanisation of the human population continues to rise [3]. Several risk factors are associated with endometrial carcinoma, such as early menarche, late menopause, unopposed oestrogen exposure, lifestyle factors, parity, obesity, demographic factors, use of oral contraceptive pills and hormone replacement therapy. However, the, molecular genetics plays a pivotal role in the pathogenesis of AEH and endometrial carcinoma [3,4]. Numerous studies have reported a list of molecular defects of clinical interest, including loss or gain of function, related to PIK3CA, Stathmin, p53, MMP-2, K-ras, PAX-2, hTERT, C-myc, survivin, RUNX1, ETV5/ERM, ER, PR-A/PR-B, HER2/neu, beta-catenin, PI3K/AKT, Fibroblasts growth factor receptor-2 and PTEN in AEH and endometrial carcinoma [5-8].

The pathogenesis of the endometrial hyperplasia has recently been simplified as endometrial hyperplasia without atypia and AEH [4]. The AEH is a precursor lesion for endometrial carcinoma type I. These two broad categories have a definite clinical implication for the treatment approaches and risk of neoplastic transformation [9]. The association between AEH and type I endometrial carcinoma type I was attempted through evidences of molecular pathology. It's been known by now that a few of molecular alterations in tumour suppressor gene and few of the cell signaling pathways, such as PI3K/AKT has been collaborated by the pathologies of AEH and endometrial carcinoma [10,11].

PTEN, a tumour suppressor gene situated at 10q23, is known to produce some certain proteins and lipids which block the phosphatases and others as one of the checkpoints for cell cycle activity especially of PI3K/AKT pathway. PTEN suppresses both cellular proliferation and differentiation by exhibiting antagonistic effect on intracellular signaling pathways induced by integrins and other growth factors. PTEN protein is also involved in cellular migration, adhesion and induces apoptosis of damaged cells molecule by different mechanisms. The various mechanisms involved are activated by overexpression of PTEN gene, which leads to increased p27 expression causing cell growth suppression through cell cycle arrest. It also activates p53 by restricting murine double minute 2 (mdm2) to cytoplasm. This mechanism provides evidences regarding dysregulation of PTEN expression contributed to cancer progression by inhibiting apoptosis and regulating pathways that accelerate cellular proliferation [9]. Therefore, PTEN becomes an important marker to be assessed in endometrial cancer type I and AEH. Reports from early 2000 by Salvesen HB et al., Pallares J et al., Doll A et al., and Lacey JV et al., have implicated loss of PTEN expression as a diagnostic marker for earliest endometrial cancer, metastatic disease, disease progression and progression of AEH to endometrial carcinoma [12-15]. The study of Okuda T et al., assessed genetics of endometrial carcinoma, which included assessment of K-ras, BRAF, Her2, beta-catenin, PMS-2, AKT, FGFR-2, along with PTEN and p53 [5]. Over the past decade, many studies have implicated endometrial tumour progression and the metastasis related to loss of PTEN expression assessed on Immunohistochemistry (IHC). The mutation in PTEN gene have also been associated with response to chemotherapy and due to loss of PTEN expression in endometrial tumours. PI3K/AKT pathway has been targeted for treatment of endometrial cancer [16-23]. Hence, the aim of the present review was to study the loss of PTEN immunoexpression in endometrial carcinoma.

## LITERATURE SEARCH

The Google Scholar and PubMed database were used to find the relevant literature on immunoexpression of PTEN in cases of endometrial carcinoma. Full-text articles in English language articles, relevant to the topic were selected.

**Inclusion criteria:** Studies evaluating the loss of IHC expression of PTEN in endometrial carcinoma, studies based on primary data search, articles published in indexed scientific journals and studies published from 2009 till the date were included in the review.

**Exclusion criteria:** Studies including other techniques for evaluating PTEN expression in endometrial carcinoma cases, duplicate publications, studies investigating populations with chronic diseases and review articles excluded from the study. The reference list of selected articles was scanned to identify additional relevant articles meeting the eligibility criteria of the present review.

## Observations

Based on the literature search, the present review included eight original studies that analysed the loss of immunostaining for PTEN in the histopathological section of endometrial carcinoma. All these studies included the cases of histological type of endometrial carcinoma [Table/Fig-1] [9,22-28]. The origin of countries for the studies were as follows: one from Canada [23], one from Egypt [9], two from India [25,27], one from Iran [22], one from Iraq [26], one from Poland [28] and one from USA [24].

| Studies | Country of origin | Type of study | Age range in years | Total no. of cases of endometrial carcinoma | Loss of PTEN immuno-expression (number and percentage) |
|---|---|---|---|---|---|
| Allithy AN et al., [9], 2022 | Egypt | Prospective | Mean age- 50.4 | 32 cases | 4 cases (12.5%) |
| Sarmadi S et al., [22], 2009 | Iran | Retrospective | - | 29 cases | 15 cases (52%) |
| Djordjevic B et al., [23], 2012 | Canada | Retrospective | 35-75 | 100 cases | 75% cases |
| Yang HP et al., [24], 2015 | USA | - | - | 148 cases | 55% cases |
| Rani E and Thukral S [25], 2019 | India | Retrospective | Mean age- 56.7 | 13 cases | 08 cases (61.54%) |
| Ali Z and Berzinji P [26], 2023 | Iraq | Correctional retrospective | 31-85 | 105 cases | 77 cases (68.8%) |
| Behera B et al., [27], 2023 | India | Observational | 35-70 | 07 cases | 07 cases (100%) |
| Brucka A and Szyłło K [28], 2013 | Poland | Observational | Mean age- 52.7 | 93 cases | 1.07% |

**[Table/Fig-1]:** Various studies depicting distribution of age, country of origin, loss of PTEN expression.

Endometrial carcinoma was more common in women aged 31 to 85 years in the studies reviewed. All the studies had variable sample sizes of endometrial carcinoma cases that underwent PTEN immunoexpression evaluation. The minimum sample size was reported by Behera B et al., (7 cases), while the maximum was reported by Yang HP et al., (148 cases) [24,27].

[Table/Fig-1] depicts the percentage of cases that showed a loss of PTEN immunoexpression. Behera B et al., observed a 100% loss of PTEN immunoexpression in 7 cases of endometrial carcinoma, followed by Djordjevic B et al., who observed a loss of PTEN in 75 cases (75%) [23]. However, studies conducted by Brucka A, Szyłło K and Allithy AN et al., reported a lesser loss of PTEN immunoexpression in endometrial carcinoma, at only 1.07% and 12.5%, respectively [9,28]. All other studies observed a loss of PTEN immunoexpression in over 50% of the cases, indicating the role of PTEN in the pathogenesis of endometrial carcinoma.

Not many studies have performed statistical analyses comparing type I endometrial carcinoma with PTEN immunoexpression. However, the studies by Sarmadi S et al., observed a definitive relationship between the loss of PTEN immunoexpression and type I endometrial carcinoma, with a p-value <0.001 [22]. Similarly, Ali Z and Berzinji P also noted significant loss of PTEN immunoexpression in their cases of type I endometrial carcinoma (p-value of 0.001) [26]. This suggests that PTEN plays an important role in the molecular pathogenesis of type I endometrial carcinoma. There is no population-based bias regarding the role of PTEN in the genesis of type I endometrial carcinoma, as evidenced by the diverse origins of the articles, which span various continents and ethnic groups.

The studies in the last decade by Djordjevic B et al., performed IHC for PTEN and observed that 75% of endometrial cancer cases were positive for the loss of immunoexpression of PTEN [23]. The grade of endometrioid tumours did not significantly correlate with the likelihood of detecting a PTEN sequence abnormality or PTEN protein loss. Yang HP et al., observed that in their IHC assay of PTEN, 55% of endometrial cancers showed PTEN positivity for loss of immunoexpression, compared to 19% of benign endometrial tissues [24]. PTEN loss was detected nearly three times as frequently in carcinoma cases. Rani E and Thukral S, evaluated PTEN immunoexpression in normal endometrial tissue, endometrial hyperplasia without atypia, AEH and endometrial carcinoma. They interpreted that decreased PTEN immunoexpression is a marker of progression from premalignant lesions to endometrial carcinoma [25]. The loss of PTEN expression occurs during the premalignant stage of the disease and continues as it progresses to carcinoma. Thus, decreased PTEN expression serves as a marker for the progression of premalignant lesions to endometrial carcinoma. It is proposed that using PTEN immunostaining in clinical settings could assist in identifying premalignant lesions that are likely to advance to carcinoma. Sarmadi S et al., observed that altered PTEN expression is a marker for differentiating normal, hyperplastic and neoplastic endometrium [22]. In contrast to the findings of the aforementioned studies, the study by Brucka A and Szyłło K suggested that PTEN immunoexpression in ectopic endometrial foci cannot be used to identify women with an increased risk of neoplastic transformation [28].

The study of Ali Z and Berzinji P assessed PTEN expression by IHC in endometrial carcinoma cases. They found that 68.8% of cases were negative for PTEN expression, while 31% showed positive PTEN expression [26]. They concluded that PTEN immunoexpression was interrelated with tumour histologic type (p-value=0.001), while no correlation was noted between PTEN and clinicopathologic characteristics. The loss of PTEN expression seen in endometrial carcinoma, especially of the endometrioid type, supports the dualistic model of endometrial carcinogenesis and suggests dysregulation of the PI3K-AKT pathway. Therefore, these patients may potentially respond to inhibitors of this pathway. Behera B et al., conducted a study on 146 patients in which IHC evaluation of PTEN expression was done. They observed that the decrease in PTEN expression was associated with the malignant features of the endometrium (p-value <0.001). Hence, this can be used as a diagnostic tool for screening of malignant and premalignant lesions of the endometrium [27].

Researches indicate that the loss of PTEN expression starts in the early stages of endometrial tumourigenesis, particularly under conditions of excessive oestrogen exposure. The PTEN inactivation begins in precancerous tissues that arise from a normal state and further PTEN damage occurs as the disease progresses to a malignant stage.

## CONCLUSION(S)

The present review concludes that one of the important molecular defects in endometrial carcinoma is the loss of tumour suppressor gene of PTEN. The IHC of PTEN on the tumour tissue will enable the distinction between the precancerous lesion of AEH and endometrial carcinoma, which have overlapping histomorphologies.

## REFERENCES

[1] ICMR [Internet]. [cited 2019]. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/Uterine_Cancer.pdf.
[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clinicians. 2021;71(3):209-49.
[3] Scott B. Advancements in endometrial cancer research in 2023. EMJ Oncol. 2024;12(1):02-13.
[4] Honda T, Urabe R, Kurita T, Kagami S, Kawagoe T, Toki N, et al. Trends in the demographic and clinicopathological characteristics in Japanese patients with endometrial cancer, 1990-2010. Int J Womens Health. 2012;4:207-12.

[5] Okuda T, Sekizawa A, Purwosunu Y, Nagatsuka M, Morioka M, Hayashi M, et al. Genetics of endometrial cancers. Obstet Gynecol Int. 2010;2010:984013.
[6] Berg A, Hoivik EA, Mjøs S, Holst F, Werner HMJ, Tangen IL, et al. Molecular profiling of endometrial carcinoma precursor, primary and metastatic lesions suggest different targets for treatment in obese compared to non-obese patients. Oncotarget. 2015;6(2):1327-39.
[7] Aguilar M, Chen H, Rivera-Colon G, Niu S, Carrick K, Gwin K, et al. Reliable identification of endometrial precancers through combined Pax2, β-Catenin, and PTEN immunohistochemistry. Am J Sur Pathol. 2022;46(3):404-14.
[8] Dobrzycka B, Terlikowska KM, Kowalczuk O, Niklinski J, Kinalski M, Terlikowski SJ. Prognosis of Stage I endometrial cancer according to the FIGO 2023 Classification taking into account molecular changes. Cancers. 2024;16(2):390.
[9] Allithy AN, Ammar IMM, Mohammed MH. Diagnostic and prognostic values of PTEN expression in functional and pathological endometrial biopsies. Asian Pac J Cancer Biol. 2022;7(1):21-27.
[10] Zheng W. Molecular Classification of Endometrial Cancer and the 2023 FIGO Staging: Exploring the challenges and opportunities for pathologists. Cancers. 2023;15(16):4101.
[11] Xia Q, Ali S, Liu L, Li Y, Liu X, Zhang L, et al. Role of ubiquitination in PTEN cellular homeostasis and its implications in GB drug resistance. Front Oncol. 2020;10:1569.
[12] Salvesen HB, Stefansson I, Kalvenes MB, Das S, Akslen LA. Loss of PTEN expression is associated with metastatic disease in patients with endometrial carcinoma. Cancer. 2002;94(8):2185-91.
[13] Pallares J, Bussaglia E, Martínez-Guitarte JL, Dolcet X, Llobet D, Rue M, et al. Immunohistochemical analysis of PTEN in endometrial carcinoma: A tissue microarray study with a comparison of four commercial antibodies in correlation with molecular abnormalities. Modern Pathology. 2005;18(5):719-27.
[14] Doll A, Abal M, Rigau M, Monge M, Gonzalez M, Demajo S, et al. Novel molecular profiles of endometrial cancer- New light through old windows. J Steroid Biochem Mol Biol. 2008;108(3-5):221-29.
[15] Lacey JV, Mutter GL, Ronnett BM, Ioffe OB, Duggan MA, Rush BB, et al. PTEN expression in endometrial biopsies as a marker of progression to endometrial carcinoma. Cancer Res. 2008;68(14):6014-20.
[16] Makker A, Goel MM. Tumour progression, metastasis, and modulators of epithelial–mesenchymal transition in endometrioid endometrial carcinoma: An update. Endocrine-Related Cancer. 2016;23(2):R85-111.
[17] Shanmugapriya M, Sudha M, Geetha P. A study of PTEN expression in endometrial hyperplasia and endometrioid type of endometrial carcinoma. Tropical J Pathol Microbiol. 2017;3(1):39-45.
[18] Ray Dr S, Jha Dr A, Afreen Islam Dr A, Sengupta Dr M. Study of prognostic and diagnostic significance of P53 and PTEN mutation in proliferative lesions of endometrium. J Current Med Res Opinion. 2020;3(08):563-69.
[19] Agarwal S, Melgandi W, Sonkar D, Ansari F, Arora S, Rathi A, et al. Epidemiological characteristics of endometrial cancer patients treated at a tertiary health center in National Capital Territory of India. J Can Res Ther. 2023;19(2):452.
[20] Raffone A, Travaglino A, Saccone G, Viggiani M, Giampaolino P, Insabato L, et al. PTEN expression in endometrial hyperplasia and risk of cancer: A systematic review and meta-analysis. Arch Gynecol Obstet. 2019;299(6):1511-24.
[21] El Kholy MA, El Kholy EA. Endometrial hyperplasia versus carcinoma: Does phosphatase and tensin homolog immunohistochemical expression differentiate between them. The Scientific Journal of Al-Azhar Medical Faculty, Girls. 2019;2(3):150-55.
[22] Sarmadi S, Izadi-Mood N, Sotoudeh K, Tavangar S. Altered PTEN expression; A diagnostic marker for differentiating normal, hyperplastic and neoplastic endometrium. Diagn Pathol. 2009;4(1):41.
[23] Djordjevic B, Hennessy BT, Li J, Barkoh BA, Luthra R, Mills GB, et al. Clinical assessment of PTEN loss in endometrial carcinoma: Immunohistochemistry outperforms gene sequencing. Modern Pathology. 2012;25(5):699-708.
[24] Yang HP, Meeker A, Guido R, Gunter MJ, Huang GS, Luhn P, et al. PTEN expression in benign human endometrial tissue and cancer in relation to endometrial cancer risk factors. Cancer Causes Control. 2015;26(12):1729-36.
[25] Rani E, Thukral S. Study of expression of PTEN in endometrium at a tertiary care centre. IJAR. 2019;902-906.
[26] Ali Z, Berzinji P. Immunohistochemical expression of PTEN (phosphatase and tension homolog) in endometrial carcinoma. Zanco J Med Sci. 2023;27(1):96-106.
[27] Behera B, Nayak J, Mohanty SR, Patro MK, Senapati SR, Dash N. Evaluation of altered PTEN expression by IHC as a diagnostic marker in hyperplastic and neoplastic endometrium observational descriptive study. SJHR-Africa. 2023;4(6):08.
[28] Brucka A, Szyłło K. Immunoexpression of the PTEN protein and matrix metalloproteinase-2 in endometrial cysts, endometrioid and clear cell ovarian cancer. Ginekol Pol. 2013;84(5):344-51.

**PARTICULARS OF CONTRIBUTORS:**
1. Junior Resident, Department of Pathology, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, India.
2. Director Professor, Department of Pathology, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Garima Chandrakar,
Shalinata PG Girls Hostel, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha-442005, Maharashtra, India.
E-mail: garimachandrakar27@gmail.com

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Sep 11, 2024
- Manual Googling: Nov 14, 2024
- iThenticate Software: Nov 16, 2024 (8%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 4

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 09, 2024**
Date of Peer Review: **Sep 25, 2024**
Date of Acceptance: **Nov 18, 2024**
Date of Publishing: **Jan 01, 2025**