REVIEW ARTICLE

The Role of PTEN Tumour Suppressor Genes in Endometrial Cancer: A Literature review

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Keywords: PTEN, Tumor Suppressor, endometrial Cancer, Genetic Mutation, P13K/AKT Pathway, Oncology;

ABSTRACT

Introduction: The PTEN gene is one of the main tumour suppressors, which is essential in regulating cell growth and preventing carcinogenesis. In endometrial cancer, mutations or loss of function of PTEN are frequently associated with disease progression, making this gene a relevant target for studies on molecular mechanisms and potential therapeutic approaches. Uncontrolled activation of the PI3K/AKT pathway, resulting from PTEN inactivation, favours cell proliferation and resistance to apoptosis, contributing to tumour aggressiveness.

Methods: This study is based on a systematic review of the scientific literature, analysing articles published between 2010 and 2025 in databases such as PubMed, Scopus and Web of Science. Studies that investigate the relationship between PTEN mutations and the development of endometrial cancer, considering molecular, clinical and therapeutic aspects, were included. The selection of articles followed strict inclusion and exclusion criteria, prioritising research with significant samples and well-established methodologies.

Results: The data analysed indicate that PTEN mutations are present in approximately 50% of endometrial cancer cases, being more frequent in high-grade tumours. These mutations compromise the function of the PTEN protein, allowing cells with DNA damage to avoid apoptosis and continue to proliferate. In addition, tumours with PTEN mutations are more resistant to conventional treatments, such as chemotherapy and radiotherapy. Recent studies suggest that inhibition of the PI3K/AKT pathway may be a promising strategy to contain tumour progression in patients with PTEN mutations.

Discussion: The presence of PTEN mutations in endometrial cancer reinforces its importance as a prognostic and therapeutic biomarker. Uncontrolled activation of the PI3K/AKT pathway contributes to exacerbated cell proliferation, resistance to apoptosis, and tumour angiogenesis, favouring cancer dissemination. Therapeutic strategies aimed at modulating this pathway are being investigated, including specific PI3K inhibitors and targeted therapies. However, challenges such as heterogeneity of mutations and the interaction of PTEN with other molecular pathways require more personalised approaches for the treatment of the disease.

Conclusion: The PTEN gene plays an essential role in regulating cell growth and preventing endometrial cancer. Its mutation or loss of function is directly related to tumour progression, therapeutic resistance, and poor prognosis of the disease. Understanding these mechanisms paves the way for the development of new therapeutic strategies, including targeted therapies and PI3K/AKT pathway inhibitors, which may improve clinical outcomes for patients. Future studies should focus on identifying biomarkers associated with PTEN and improving targeted therapies to optimise the management of endometrial cancer.

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What do we already know about this topic?
The PTEN gene is one of the main tumor suppressors, responsible for regulating cell growth and preventing the uncontrolled proliferation of malignant cells. In endometrial cancer, its mutation or loss of function is associated with tumor progression and a worse prognosis of the disease. PTEN's action is directly linked to the PI3K/AKT signaling pathway, which governs processes such as cell proliferation, apoptosis, and metabolism. When functional, PTEN limits this pathway, preventing excessive cell growth. However, genetic alterations in PTEN can compromise this function, resulting in hyperactivation of the PI3K/AKT pathway, favoring tumor multiplication and resistance to conventional therapies. Studies indicate that mutations in PTEN are common in endometrioid tumors, being detected in 34% to 55% of cases. These mutations can occur through genetic deletions, point mutations, or epigenetic modifications, such as hypermethylation of the gene promoter, which silences its expression and contributes to disease progression. Furthermore, the absence of PTEN may stimulate tumor angiogenesis, facilitating cancer dissemination. PTEN has been investigated as a prognostic biomarker, enabling personalized approaches to the treatment of endometrial cancer. Targeted therapies, such as PI3K/AKT pathway inhibitors, are being explored to curb tumor progression and improve patient outcomes. Despite advances in the understanding of PTEN, challenges remain in implementing effective treatments. The heterogeneity of mutations and their interaction with other molecular pathways require innovative approaches, including immunotherapy and epigenetic modulation. The study of PTEN remains essential to improve therapeutic strategies and develop more effective and personalized treatments for endometrial cancer.

What is the main contribution to Evidence-Based Practice from this article?
The main contribution of this article to evidence-based practice is the detailed analysis of the role of the PTEN gene in endometrial cancer, consolidating recent scientific findings and their clinical implications. By bringing together data from studies on mutation frequency, prognostic impact, and therapeutic approaches, the article helps to understand the molecular mechanisms involved in tumor progression and response to treatment. In addition, it highlights the potential of PTEN as a prognostic and therapeutic biomarker, which may contribute to the personalization of clinical strategies. The discussion of PI3K/AKT pathway inhibitors and other targeted therapies reinforces the need for more effective and individualized approaches for patients with endometrial cancer, in line with precision medicine guidelines. With this information, healthcare professionals can make more informed decisions about diagnosis, prognosis, and choice of treatments, promoting a more targeted and effective approach for patients with PTEN mutations.

What are this research's implications towards health policy?
The research deepens the understanding of the molecular mechanisms of carcinogenesis, highlighting the PI3K/AKT pathway and its role in tumor proliferation. The analysis of PTEN mutations contributes to theoretical models on the interaction between genetic and epigenetic alterations, influencing cancer progression. In addition, it reinforces the idea of biomarkers as prognostic predictors, allowing a refinement in the molecular classification criteria for endometrial cancer. The identification of PTEN mutations can be used to stratify patients, allowing personalized approaches, such as the use of PI3K/AKT pathway inhibitors. The research also suggests that PTEN analysis can improve the predictability of response to conventional therapies, helping physicians make more accurate treatment decisions. In addition, it can influence the development of new therapeutic protocols, incorporating targeted therapies and epigenetic modulators to increase the efficacy of treatments. This study reinforces the need for public policies focused on personalized medicine, promoting access to genetic tests that can identify PTEN mutations and guide more effective treatments. It also highlights the importance of investing in translational research, allowing scientific advances to be rapidly integrated into medical practice. In addition, it can influence guidelines on the incorporation of new therapies into the health system, ensuring innovative treatments for patients with endometrial cancer. The impact of this article can contribute to new therapeutic approaches, influencing both drug development and policy formulation aimed at personalized oncology.

Authors' Contributions Statement:
La Paz, Caio Siqueira was the main author of the manuscript, contributing to the writing of the introduction, methodology, results and discussion. Viana, Laíza Virnia Cortes was a co-author of the manuscript, contributing to the writing of the introduction, results and conclusion. Bueno, Maísa Marques was a co-author of the manuscript, contributing to the writing of the introduction, discussion and results.

Introduction

Endometrial hyperplasia (EH) is an irregular proliferation of the endometrial glands and is involved in the development of endometrioid-type endometrial cancer (EC), which is the most common gynecological malignancy in the Western world. Since EH can be a precancerous lesion as well as a polyclonal proliferation caused by the unopposed action of estrogens, its malignant potential is highly variable, with progression rates to EC ranging from less than 1% to more than 40% (Mester & Eng, 2020). To choose an appropriate treatment, a different diagnosis between benign and premalignant EH is necessary. In particular, benign EH requires only observation or progestins when symptomatic, while premalignant EH requires hysterectomy or progestins for conservative management in selected cases (Mester & Eng, 2020). The 2014

World Health Organisation (WHO) classification system differentiates atypical (premalignant) EH from EH without atypia (benign) based on the presence of cytologic atypia. Previous WHO systems also considered the complexity of glandular architecture for the classification of HE, although its impact on malignant potential was not well defined (WHO, 2002). For these reasons, there has been great interest in the literature on less expensive prognostic markers in HE. The Phosphatase and Tensin Homolog (PTEN) tumour suppressor protein has probably been the most studied marker, since the PTEN gene is the most commonly mutated in endometrial carcinogenesis (Tan et al., 2012).
At the 2016 ESMO-ESGO-ESTRO Consensus Conference on EC, immunohistochemical evaluation of PTEN was recommended to recognize premalignant EH, which often shows a loss of protein expression (Tan et al., 2012).
EC has a multifactorial etiology, being influenced by hormonal, genetic, and environmental factors. Continuous estrogenic stimulation without opposition from progesterone is one of the main mechanisms involved in endometrial carcinogenesis. Risk factors include obesity, diabetes mellitus (DM), arterial hypertension (AH), early menarche, late menopause, nulliparity, and prolonged use of estrogen-only hormone therapy. In addition, genetic syndromes such as Lynch syndrome significantly increase the risk of developing this type of cancer (Walsh et al., 2011).
In Brazil, the incidence of EC has increased in recent years. In 2018, it was estimated that there would be 6.22 new cases for every 100,000 Brazilian women. Projections indicate that this number could reach 9,372 new cases in 2025 and 11,963 in 2035 (INCA, 2024).
Compared to other Latin American countries, the incidence of cervical cancer in Brazil is relatively high, especially due to the increase in obesity and population ageing. In developed countries, such as the United States and the United Kingdom, the incidence tends to be higher due to longer life expectancy and the prevalence of risk factors such as obesity and sedentary lifestyle (INCA, 2024).
Studies indicate that the number of cancer cases in the world could increase by 77% by 2050, reaching approximately 35 million new diagnoses annually. This growth is associated with the increase in the elderly population and greater exposure to risk factors such as smoking, obesity, and pollution (INCA, 2024).
In Brazil, the incidence of cancer is also expected to increase significantly. It is estimated that the number of new cancer cases in the country could double by 2050, exceeding 1.4 million annual diagnoses. Furthermore, cancer mortality in Brazil could increase by 98.6% by 2050, reaching 554,000 deaths per year (INCA, 2024).
Although there is no specific projection for EC in these studies, the general trend of increasing cancer cases suggests that this neoplasm may also grow in the coming years, especially due to population ageing and the increase in obesity, which are important risk factors for the disease (INCA, 2024).

The PTEN gene

The PTEN gene is a tumour suppressor gene, essential for regulating cell growth and preventing tumour development. It encodes a protein that acts in the PI3K/AKT signalling pathway, controlling processes such as cell proliferation, survival, and metabolism (Ho, Cruise, Dowling, & Stambolic, 2020).
When PTEN is functional, it prevents excessive activation of this pathway, preventing uncontrolled cell growth. However, mutations or inactivation of the PTEN gene can lead to hyperactivation of the PI3K/AKT pathway, favouring cell proliferation and contributing to

the development of several types of cancer, including breast, prostate, and endometrial cancer (Ho, Cruise, Dowling, & Stambolic, 2020).

In addition to its role in oncology, mutations in PTEN are associated with Cowden Syndrome, a rare genetic condition that increases the risk of benign and malignant tumours in different organs (Ho, Cruise, Dowling, & Stambolic, 2020).

The function of PTEN in counteracting the activity of the oncogenic PI3K signalling pathway provides an obvious molecular mechanism to explain PTEN's function in tumour suppression (Maehama and Dixon 1999). However, several anti-PI3K agents have universally failed to combat the growth of PTEN-deficient tumours, implicating non-PI3K aspects of PTEN function in tumour suppression (Juric et al. 2015, Le et al. 2016). Despite the frequent detection of nuclear PTEN loss in various cancer cell types, the possibility of PTEN nuclear function involvement in tumour suppression has only recently been realised. Many components of the PI3K pathway are found in the nucleus, such as PI3K, AKT, and PDK1; therefore, it was reasonable to hypothesise that PTEN may act as a lipid phosphatase in the nucleus (Déléris et al. 2006). However, although nuclear pools of PIP3 also exist, they are insensitive to the lipid phosphatase activity of PTEN and are therefore unlikely to feature in nuclear PTEN functions (Lindsay et al., 2006; Baak et al., 2005).

Mutation in the PTEN gene associated with Cowden syndrome and EC

This syndrome affects 1 in 200,000 people and is associated with a predisposition to breast, thyroid, kidney, endometrial, and colon cancer, as well as melanoma. EC occurs in 21% to 28% of these women and usually develops at a very early age. Although it is a very rare syndrome, the diagnostic criteria are clinically recognizable and the patient usually presents with typical morphological findings: macrocrania (percentile greater than 97), facial tricholemmomas, oral papillomas, and palmoplantar keratosis. EC, like breast cancer, follicular thyroid cancer, and macrocrania, is a major criterion for Cowden syndrome (Ho, Cruise, Dowling, & Stambolic, 2020; Mester & Eng, 2020).

Studies indicate that mutations in the PTEN gene are found in approximately 50% of EC cases. These mutations can result in the loss of PTEN protein function, allowing tumour cells to grow unchecked. Furthermore, the absence of PTEN can increase the resistance of cancer cells to certain treatments, making the disease more aggressive (Ho, Cruise, Dowling, & Stambolic, 2020).

PTEN mutation can occur through different mechanisms, including acquired somatic mutations, genetic deletions, epigenetic modifications, and inherited alterations. These mutations lead to the loss of PTEN protein function, resulting in uncontrolled activation of the PI3K/AKT signalling pathway, which regulates cell growth and cell survival (Ho, Cruise, Dowling, & Stambolic, 2020).

Somatic mutations in PTEN occur throughout life and are acquired by endometrial cells due to environmental factors, such as chronic inflammation, prolonged exposure to estrogen without progesterone opposition, and DNA damage caused by external agents. These mutations prevent PTEN from exercising its function of controlling the cell cycle, allowing defective cells to continue to multiply (Walsh et al., 2011; Mester & Eng, 2020).

In some cases, there is a complete loss of the PTEN gene, preventing the production of the tumour suppressor protein. This results in excessive activation of the PI3K/AKT pathway, favouring uncontrolled cell proliferation and

resistance to apoptosis (Ho, Cruise, Dowling, & Stambolic, 2020).
In addition to genetic mutations, epigenetic alterations can silence PTEN expression without directly modifying its DNA sequence.
Methylation of the PTEN gene promoter can reduce its activity, preventing it from properly regulating cell growth (Lacey et al., 2008).
The absence or dysfunction of PTEN in EC leads to a series of cellular alterations that favor tumor progression, such as accelerated cell proliferation, where without PTEN regulation, cells continue to divide uncontrollably; resistance to apoptosis, where tumor cells become more resistant to programmed cell death, allowing their prolonged survival; increased angiogenesis, where the tumor develops new blood vessels to sustain its growth and spread to other tissues; and therapeutic resistance, where tumors with PTEN mutations may be more resistant to conventional treatments, such as chemotherapy and radiotherapy (Ho, Cruise, Dowling, & Stambolic, 2020).
Identification of PTEN mutations may be useful for personalised therapeutic strategies, including inhibitors of the PI3K/AKT pathway, which seek to block tumour progression. In addition, recent research explores targeted therapies that restore PTEN function or modulate its activity to prevent cancer growth (Ho, Cruise, Dowling, & Stambolic, 2020).

Methodology

A literature review was conducted, searching for articles in databases such as PubMed, Scopus, Web of Science and SciELO, and using the following descriptors: PTEN and Endometrial Cancer, Tumour suppressor genes and endometrial carcinoma and P13/AKT pathway and PTEN mutations. Inclusion and exclusion criteria were established to ensure the relevance of the studies analysed. The inclusion criteria were articles published in the last 10 years, clinical and experimental studies, systematic reviews and meta-analyses that addressed the relationship between PTEN mutations and EC. On the other hand, articles with inadequate methodology, studies with very small samples or publications without peer review were excluded.
After selecting the studies, data extraction and analysis began, where the articles were examined for the methodology used, main results and conclusions. The information obtained was organised into categories, such as: Molecular mechanisms of PTEN in EC, analysing how mutations in the gene impact the PI3K/AKT pathway and favour tumour proliferation. The impact of mutations on disease prognosis, identifying patterns that influence cancer aggressiveness and response to treatment. Targeted therapies based on the P13K/AKT pathway, exploring new therapeutic approaches that aim to modulate PTEN activity to contain tumour progression.

Results

Loss of PTEN expression in EH is significantly associated with increased risk of EC. These findings may be expected since the PTEN mutation is known to be involved in endometrial carcinogenesis. Among the four molecular categories of EC identified by the Cancer Genome Atlas Research Network ('ultramutated', 'hypermutated' and 'low copy number', which are predominantly endometrioid, and 'high copy number', most of which are serous), PTEN mutations were found in 94%, 88%, 77% and 15%, respectively.
Furthermore, several studies have reported a higher rate of PTEN loss in EC compared with EH suggesting a prognostic significance of PTEN (Murali et al., 2019, Yen, Wang, Fader, Shih, & Gaillard, 2020). The association of PTEN loss with EC risk is significant only when a short

follow-up (less than 1 year) is considered. Several studies have indicated that an EC diagnosed within 1 year after the diagnosis of EH should be considered as already present at the time of EH biopsy, due to the typically slow growth of EC (Travaglino et al., 2019; Baak & Mutter, 2005). Thus, PTEN loss in EH predicts the presence of a coexisting EC rather than the progression of EH to EC. The reason may be that PTEN status does not affect the responsiveness of EH and EC to progestins (Lacey et al., 2010), demonstrating similar results between different PTEN-null and PTEN-positive samples in long-term treated patients. Loss of PTEN expression alone is not sufficient to trigger malignant transformation. Indeed, Baak et al. (2005) showed that endometrial glands with PTEN loss on immunohistochemistry but normal histomorphology tend to regress spontaneously in most cases (Lacey et al., 2010). On the other hand, atypical EH present several genetic alterations (Kurman, Kaminski & Norris, 1985), which may determine progression to EC when combined with PTEN loss. Lacey et al. (2010) reported that the combination of cytologic atypia and PTEN loss predicts coexisting cancer better than cytologic atypia alone (Kurman, Kaminski & Norris, 1985). Given these observations, it is questionable how PTEN assessment can influence the management of patients with atypical HE, regarding the risk of concomitant cancer. The results indicate that a mutation in the PTEN gene or loss of function is strongly associated with tumour progression and resistance to conventional treatments. PTEN is a tumour suppressor gene that negatively regulates the PI3K/AKT signalling pathway, preventing uncontrolled cell proliferation and promoting apoptosis. When there are mutations in this gene, there is excessive activation of this pathway, favouring tumour growth and cancer cell survival.

Studies show that PTEN expression is reduced in a significant portion of EC cases, especially in high-grade tumours. This reduction can occur through different mechanisms, including somatic mutations, genetic deletions, and epigenetic modifications, such as methylation of the gene promoter.

The presence of PTEN mutations is associated with more aggressive tumours and a lower response to conventional therapies. Patients with these mutations have a higher risk of disease recurrence and shorter overall survival. In addition, the absence of PTEN can contribute to resistance to treatments such as chemotherapy (CT) and radiotherapy (RT), making clinical management more challenging. In addition to genetic mutations, studies indicate that hypermethylation of the PTEN promoter can silence its expression, preventing its suppressive function. This epigenetic alteration is one of the mechanisms that contribute to the progression of EC, allowing defective cells to proliferate uncontrollably.

The identification of PTEN mutations has been explored as a potential prognostic and therapeutic biomarker. Recent research has investigated the use of PI3K/AKT pathway inhibitors as a strategy to block tumour progression in patients with PTEN mutations. In addition, targeted therapies that modulate PTEN activity are being developed to improve treatment response and increase patient survival.

Discussion

The PTEN gene plays an essential role in maintaining the balance of cell growth and protecting against tumor development. In EC, its mutation or inactivation is often associated with disease progression, making it a relevant focus for research into the mechanisms of carcinogenesis and the development of new

therapeutic approaches.
PTEN acts as a negative regulator of the PI3K/AKT signalling pathway, which controls fundamental processes such as cell proliferation, survival, and apoptosis. When functional, PTEN limits the activation of this pathway, preventing excessive cell growth. However, genetic alterations in this gene can result in hyperactivation of the PI3K/AKT pathway, promoting uncontrolled cell division and significantly contributing to the development of EC.
Studies indicate that mutations in the PTEN gene are found in approximately 50% of EC cases. These mutations can result in the loss of PTEN protein function, allowing tumour cells to grow uncontrollably. Furthermore, the absence of PTEN may increase the resistance of cancer cells to certain treatments, making the disease more aggressive.
The presence of PTEN mutations is associated with more aggressive tumours and a lower response to conventional therapies. Patients with these mutations have a higher risk of disease recurrence and shorter overall survival. Furthermore, the absence of PTEN may contribute to resistance to CT and RT treatments, making clinical management more challenging.
Another relevant aspect is the influence of PTEN on tumour angiogenesis, a process by which the tumour develops new blood vessels to sustain its growth and spread to other tissues. Uncontrolled activation of the PI3K/AKT pathway, caused by PTEN mutation, may stimulate the formation of new blood vessels, favouring the spread of cancer to adjacent organs.
In addition to genetic mutations, studies indicate that hypermethylation of the PTEN promoter may silence its expression, preventing its suppressive function. This epigenetic alteration is one of the mechanisms that contribute to the progression of EC, allowing defective cells to proliferate unchecked.
The epigenetic regulation of PTEN can also be influenced by environmental and hormonal factors. Prolonged exposure to estrogen without opposition from progesterone can affect PTEN expression, increasing the risk of developing EC.
The identification of PTEN mutations has been explored as a possible prognostic and therapeutic biomarker. Recent research is investigating the use of PI3K/AKT pathway inhibitors as a strategy to block tumour progression in patients with PTEN mutations. In addition, targeted therapies that modulate PTEN activity are being developed to improve treatment response and increase patient survival.
Despite advances in understanding the role of PTEN in EC, there are still challenges in implementing effective therapeutic strategies. The heterogeneity of PTEN mutations and their interaction with other molecular pathways require more personalised approaches to the treatment of the disease. Future studies should focus on developing new targeted therapies, including epigenetic modulators and immunotherapies, that can restore PTEN function or block its negative effects on tumour progression.

Conclusion

Research into the role of the PTEN gene in EC reveals its importance as an essential tumour suppressor, regulating the PI3K/AKT pathway and preventing uncontrolled cell growth. Mutation or loss of function of this gene is directly associated with tumour progression, therapeutic resistance, and worse disease prognosis.
Studies indicate that PTEN inactivation contributes to exacerbated cell proliferation,

resistance to apoptosis, and tumour angiogenesis, favouring cancer dissemination. In addition, epigenetic alterations, such as hypermethylation of the PTEN promoter, can silence its expression, rendering it functionally inactive and worsening disease progression. In this scenario, the identification of PTEN mutations has been explored as a prognostic and therapeutic biomarker, allowing more personalised approaches in the treatment of EC. Targeted therapies, such as PI3K/AKT pathway inhibitors, are being investigated to contain tumour progression and improve clinical outcomes for patients.

Despite advances in understanding the role of PTEN, there are still challenges in implementing effective therapeutic strategies. The heterogeneity of mutations and their interaction with other molecular pathways require innovative approaches that combine targeted therapies, immunotherapy and epigenetic modulation, enabling more effective treatment with less toxicity.

Therefore, the study of PTEN remains essential for understanding the mechanisms of endometrial cancer and for developing new therapeutic strategies that can positively impact patients' clinical outcomes. Continued research on biomarkers associated with PTEN and the improvement of targeted therapies may represent a major advance in the fight against this neoplasia.

Abbreviations

EC - Endometrial Cancer, DM - Diabetes Mellitus, EH - Endometrial Hyperplasia, AH - Arterial Hypertension, WHO - World Health Organization, PTEN - Phosphatase and Tensin Homolog, CT - Chemotherapy, RT - Radiotherapy.

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