THE RELATIONSHIP BETWEEN ENDOMETRIOSIS AND MALIGNANT THYROID NEOPLASMS: A SYSTEMATIC REVIEW

A relação entre endometriose e neoplasia maligna da tireoide: uma revisão sistemática

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ABSTRACT

Objectives: endometriosis is a chronic inflammatory disease affecting an estimated 10-15% of reproductive-aged women. Thyroid cancer, predominantly occurring in women, most commonly presents between the ages of 45 and 64. In the context of this gender overlap, existing evidence suggests a potential relationship between endometriosis and thyroid cancer. This study aims to explore this possible relationship. **Methods:** this systematic review followed the structured approach outlined in the PRISMA 2020 checklist for study selection. Inclusion criteria focused on studies examining the association between endometriosis and thyroid cancer, excluding case reports and retrospective studies with fewer than ten cases. PubMed was the primary database used for the search, employing the terms "endometriosis," "thyroid cancer," and "endometriosis and thyroid cancer." The studies were evaluated between October 2023 and April 2024. **Results:** the PubMed search yielded 20 studies, with an additional eight studies identified from the reference lists of previously included studies. Following a comprehensive review, 12 articles met the eligibility criteria and were included in the review. Data primarily derived from two meta-analyses and one large retrospective study converged on an estimated 33% to 39% increased risk for women with endometriosis to develop thyroid cancer later in life. **Discussion:** although evidence points to a possible association between endometriosis and thyroid cancer, potentially influenced by female sex hormones, the observed increase in non-gynecological cancers among endometriosis patients suggests additional factors may contribute to the elevated cancer risk. Study limitations, including a predominance of retrospective and cross-sectional designs, significant risk of bias, and high heterogeneity, limit definitive conclusions and causal interpretations. Further research using robust prospective designs is needed to clarify the underlying mechanisms and to guide clinical protocols for improved management of patients with endometriosis.

Palavras-chave: endometriosis, thyroid cancer, female sex hormones, systematic review.

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INTRODUCTION

Endometriosis is a chronic inflammatory disease that affects an estimated 10-15% of reproductive-aged women. It is caused by the presence of tissue similar to the endometrium, including glandular and stromal components, outside the uterine cavity. The disease is classified into four stages, ranked according to severity: stage I includes mild cases, while stage IV indicates the most severe forms[1].

Thyroid cancer is a condition that mainly affects women, with a female-to-male ratio of 3:1, most commonly occurring between the ages of 45 and 64. Over the last three decades, there has been a 300% increase in the incidence of this cancer, mainly due to a rise in cases of papillary thyroid cancer[2].

Due to this epidemiological overlap, recent studies have sought to analyze the potential relationship between endometriosis and thyroid cancer[3-5]. This possible association may have important clinical implications, such as a potential indication to investigate thyroid nodules in patients with endometriosis thoroughly. This study aims to explore this association further and to provide valuable insights for physicians managing these conditions.

METHODS

This study is a structured literature review conducted using PubMed as the database for study search and selection. The search terms were "endometriosis," "thyroid cancer," and "endometriosis and thyroid cancer." No time restrictions were applied to the search. The articles identified were screened in three stages: title review, abstract review, and full-text review. Additional studies were included by reviewing the reference list of a previously included study. Studies without available full-text manuscripts, case reports, and retrospective studies with fewer than 10 cases were excluded. There were no language restrictions for study search or selection.

Data were extracted from three studies: two meta-analyses and one retrospective study. The remaining selected studies provided additional information to discuss the topic further and explore this systematic review's academic and clinical significance.

Two medical students (in their third and 11th periods, respectively) and a head and neck surgeon and professor of medicine with 36 years of experience reviewed and analyzed the articles between October 2023 and April 2024.

RESULTS

Twenty studies, all in English, were retrieved from PubMed searches covering the 16 years from 2007 to 2023. Eight more were identified from the reference list of full-text manuscripts. During the screening process, 16 studies were excluded, resulting in 12 studies being included in this review (see **Figure 1** for the PRISMA flowchart of study selection and **Table 1** for a list of included studies).

Kvaskoff *et al.*'s[3] meta-analysis, which included five studies about thyroid cancer, reported a Standardized Rate Ratio (SRR) of 1.39 (95% CI: 1.24–1.57), indicating that patients with endometriosis have a 39% increased risk of developing malignant thyroid neoplasms later in life compared to women without endometriosis. Likewise, Gandini *et al.*'s[4] meta-analysis found an SRR

TABLE 1 - List of studies included included in the review of endometriosis and thyroid cancer association

STUDY'S AUTHORS	STUDY DESIGN	SAMPLE SIZE/ NUMBER OF STUDIES INCLUDED (META-ANALYSIS)	YEAR OF PUBLICATION
Mehedintu *et al.*[1]	Review	N/A	2014
Seib *et al.*[2]	Review	N/A	2019
Kvaskoff *et al.*[3]	Systematic review and meta-analysis	5 studies	2021
Gandini *et al.*[4]	Systematic review and meta-analysis	5 studies	2019
Melin *et al.*[5]	Retrospective study	63,630	2007
Saunders *et al.*[6]	Review	N/A	2021
Bouic *et al.*[7]	Review	N/A	2023
Chmielik *et al.*[8]	Review	N/A	2018
Huang *et al.*[9]	Cross-sectional (genetics)	989	2022
Lamartina *et al.*[10]	Review	N/A	2020
Braganza *et al.*[11]	Prospective cohort	70,047	2014
Kvaskoff *et al.*[12]	Systematic review	N/A	2015

of 1.38 (95% CI: 1.17–1.63), representing a 38% increased risk of thyroid cancer in patients with endometriosis.

Additionally, Melin *et al.*'s5 retrospective study found a Standardized Incidence Ratio (SIR) of 1.33 (95% CI: 1.02–1.70), indicating a 33% higher incidence of thyroid cancer in the study sample compared to what would be expected in the general population.

DISCUSSION

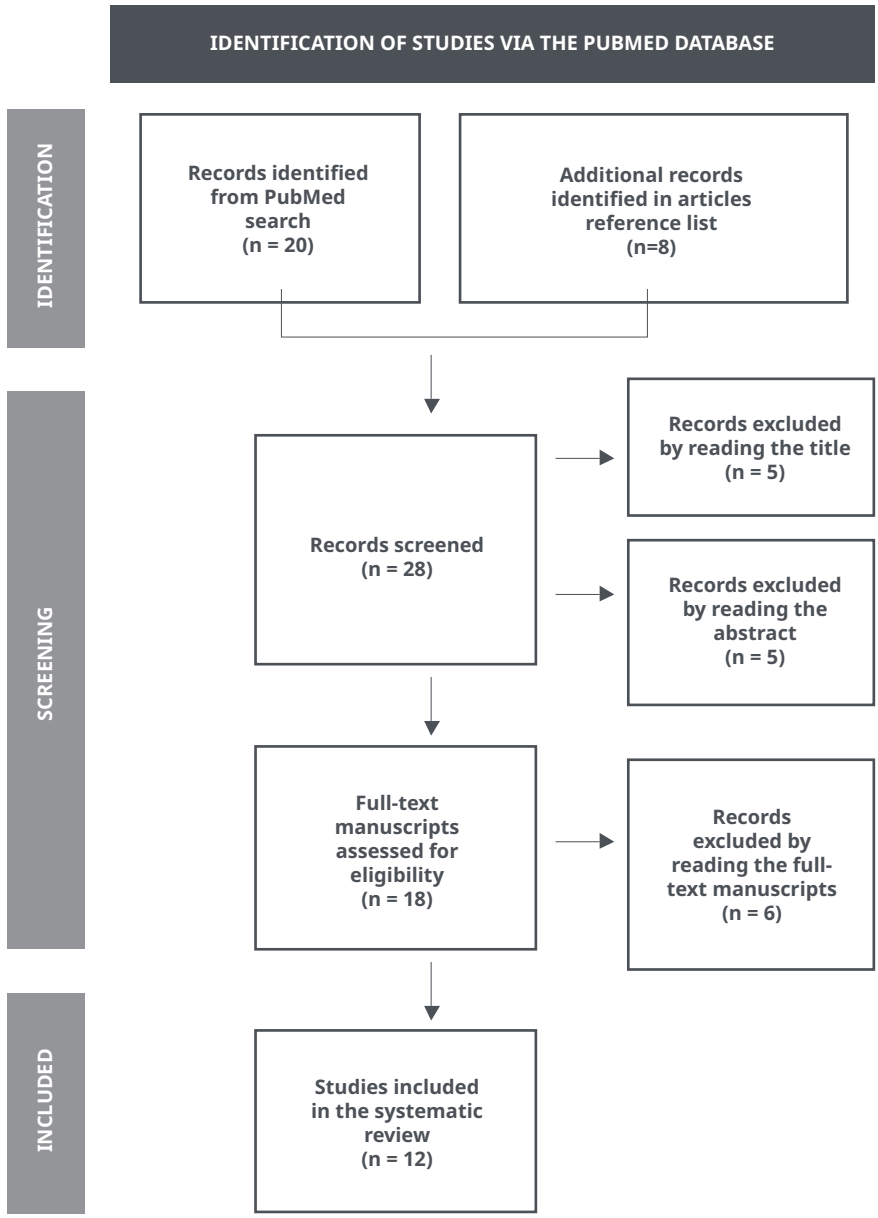
Endometriosis is a chronic condition characterized by the dissemination of endometrium-like tissue to locations outside the uterine cavity. The most common sites of ectopic tissue implantation include the ovaries, cul-de-sac, and uterosacral ligaments[1,6]. Surgery remains the gold-standard method for categorizing the disease into four stages of severity[6].

Current treatments of endometriosis have significant limitations in effectiveness. Therapeutic approaches include surgery to excise ectopic endometrial lesions, along with medications aimed at hormonal modulation. However, these interventions do not reliably prevent disease recurrence[6,7]. Repeated surgeries may be necessary in cases of recurrence, which can negatively impact patients' quality of life[7].

The etiology of endometriosis remains unclear. Several theories have been proposed, including the roles of lifestyle factors, environmental influences, celomic metaplasia, and immune system dysfunctions[1,7]. This uncertainty highlights the need for future research aimed at improving the prognosis and management of the disease.

Thyroid cancer, on the other hand, is the most common endocrine malignancy worldwide, with incidence rates increasing in recent decades[2,8]. It predominantly affects women, with a female-to-male ratio of 3:12. The five main types of thyroid tumors are papillary, follicular, poorly differentiated, anaplastic, and medullary carcinomas[8]. Known risk factors for thyroid cancer include obesity, certain benign thyroid conditions (e.g., chronic thyroiditis and goiter), female sex hormones, growth factors (e.g., insulin-like growth factor and chronic thyroid-stimulating hormone

FIGURE 1 - PRISMA 2020 flow diagram showing the process for study selection



hyperstimulation), dietary factors (e.g., low iodine intake), smoking, physical inactivity, and childhood exposure to ionizing radiation[9,10].

Screening approaches to each type of thyroid cancer vary. For medullary thyroid cancer, genetic testing is recommended primarily in cases where multiple endocrine neoplasia type 2 (MEN2) is suspected, due to its association with RET gene mutations. For well-differentiated thyroid cancers, such as papillary and follicular thyroid carcinoma, the U.S. Preventive Services Task Force does not recommend routine screening, as the potential risks outweigh the benefits[11]. Lamartina *et al.*[10] suggest that neck palpation by a skilled physician could serve as an intermediate approach between no screening at all and highly sensitive ultrasonography. However, further large-scale studies are needed to support this recommendation.

As a higher incidence of thyroid cancer has been observed in women with an earlier onset of menarche and

late menopause, female sex steroid hormones may be involved in the elevated occurrence of thyroid cancer in these patients. Experimental studies have shown that estradiol can promote the proliferation of thyroid cells in vitro. Additionally, individuals diagnosed with thyroid cancer have shown elevated post-diagnosis serum estradiol levels and decreased progesterone blood concentrations[12].

Braganza *et al.*[12] investigated the association between benign breast and gynecological conditions, reproductive and hormonal factors, and the risk of thyroid cancer. The study included 70,047 women aged 50 to 78, which were followed over 11 years, during which 127 women were diagnosed with thyroid cancer. The results indicated that older age at natural menopause, a higher estimated number of lifetime ovulatory cycles, a greater number of childbirths, and the presence of uterine fibroids were associated with an increased risk of thyroid cancer. However, although the study employed a prospective design, endometriosis was not isolated as the primary exposure variable. Nonetheless, these findings provide insights into the potential effects of female sex hormones on thyroid cancer, even though they do not specifically address the impact of endometriosis.

The evidence that gynecological diseases and female sex hormones may be linked to thyroid cancer raises the question of whether endometriosis, a common benign gynecological condition, might also affect the incidence of thyroid cancer. As mentioned, a retrospective study by Melin *et al.*[5] investigated the incidence of various cancers in 65,349 patients with endometriosis. In addition to finding a SIR of 1.33 for thyroid cancer, the authors reported a higher incidence of other non-gynecological cancers in patients with endometriosis, including renal cancer, brain tumors, and malignant melanoma. These findings suggest that women with endometriosis may be at an elevated risk of various cancer types, not only gynecological tumors or cancers with a known higher incidence in women. Therefore, factors beyond female sex hormones may contribute to this increased risk of thyroid cancer.

Although the meta-analysis by Kvaskoff *et al.*[3] reported a strong association between endometriosis and increased risk of thyroid and ovarian cancer—suggesting a possible role of sex hormones given the disproportionately higher incidence of thyroid cancer in women—the authors also noted an increase, although minimal, in the risk for other non-gynecological cancers, such as cutaneous melanoma. However, the authors highlighted that most studies included in the meta-analysis had a severe or critical risk of bias and high heterogeneity. These limitations significantly hinder definitive conclusions about the relationship between endometriosis and cancer risk, particularly regarding the influence of sex hormones.

In contrast to the other two studies, Gandini *et al.*'s[4] meta-analysis reported no increase in melanoma risk while finding a moderate positive association with thyroid and endometrial cancer. The authors also observed no between-estimates heterogeneity (I^2 = 0%) for thyroid cancer studies and no publication bias, further strengthening the evidence for an association between endometriosis and thyroid cancer. However, the reliance on data primarily from retrospective or cross-sectional studies makes it challenging to draw definitive conclusions and establish causality.

Besides its association with various cancers, including thyroid cancer, endometriosis has also been linked to benign conditions such as autoimmune diseases and allergies[13]. However, evidence from a previous cross-sectional study indicates that benign thyroid conditions, such as autoimmune thyroid disorders, hypothyroidism, and hyperthyroidism, are not more frequent in patients with endometriosis than in the general population[14].

This study has several significant limitations. First, the small number of studies included - only 12 - highlights the need for further research to better elucidate the association between endometriosis and thyroid cancer. This limited number poses challenges in building a robust dataset for a comprehensive systematic review. Moreover, specific data on different types of thyroid cancer associated with this increased risk are still not available. Second, only one study employed prospective designs[12] but did not focus on endometriosis as the primary exposure variable. This is a significant limitation, as prospective studies are essential for establishing causality. On the other hand, retrospective studies may be prone to biases such as recall bias, which complicate the ability to draw definitive conclusions.

In summary, this review's main finding suggests an association between endometriosis and thyroid cancer. Studies converged on a 33% to 39% increased risk for women with endometriosis to develop thyroid cancer later in life. Understanding the relationship between these two conditions could ultimately benefit patients by creating enhanced clinical protocols and improving outcomes. However, given the limited data on this subject, more research is needed to fully understand this association and its underlying mechanisms.

CONFLICT OF INTEREST

The authors attest they have no conflict of interest to declare.

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