

Review

# Endometriosis-associated Extraovarian Malignancies: A Challenging Question for the Clinician and the Pathologist

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**Abstract.** Endometriosis is an estrogen-dependent disease, which affects 10% of women in the reproductive age. Malignant transformation is an uncommon event, which affects approximately 0.7-2.5% of women, and, when it occurs, it involves ovarian and extraovarian sites in 75% and 25% of the cases, respectively. Endometriosis correlates with presentation of clear cell and endometrioid carcinoma of the ovary. Activation of phosphatidylinositol 3-kinase (PIK3) – protein kinase B (AKT) – mammalian target of rapamycin (mTOR) pathway, aberrant chromatin remodeling due to AT-rich interactive domain-containing protein 1A (ARID1A) mutation and inactivation of estrogen receptor- $\alpha$  signaling seem to play a major role in the carcinogenesis. To date, little data are available regarding endometriosis-associated extraovarian malignancies. The aim of the present study was to review the clinical, pathological and prognostic features of endometriosis-related neoplasms arising from extraovarian sites, with particular focus on intestinal malignancies, urinary tract malignancies and tumors arising from surgical scars.

Endometriosis is an estrogen-dependent chronic disease, which affects 10% of women in the reproductive age, 21-50% of those with infertility, and up to 82% of those with chronic pelvic pain (1, 2). An increase in the prevalent cases

of endometriosis from 5.66 million in 2012 to 5.86 million in 2022 has been hypothesized (3). Although the etiology is still unclear, environmental factors and especially endocrine-disrupting chemicals seem to play a pathogenetic role (4, 5). A meta-analysis of 30 epidemiological studies showed that the odds ratio (OR) for the risk of developing endometriosis associated with the exposure to four endocrine-disrupting chemicals was 1.41 [95% Confidence Interval (CI)=1.23-1.60], ranging from 1.58 (95% CI=1.18-2.12) for polychlorinated biphenyls, to 1.40 (95% CI=1.02-1.92) for organochlorine pesticides and to 1.27 (95% CI=1.00-1.60) for phthalate esters, while bisphenol A appeared to have no significant association (4).

Malignant transformation of endometriosis happens in 0.7-2.5% of women, and, when it occurs, it involves the ovary in approximately 75% of the cases (5, 6). The pathological criteria for the diagnosis of endometriosis-associated tumors have been reported for the first time in 1927 by Sampson (7). In brief, the evidence of endometriosis near the tumor, the demonstration of cancer arising from endometriosis and not elsewhere, and the presence of tissue similar to the endometrial stroma surrounding characteristic epithelial glands, are considered the most reliable criteria for demonstrating a link between endometriosis and malignant tumors. Moreover, another criterion was introduced in 1953 by Scott (8), who suggested that the histological transition between benign endometriotic foci and malignant neoplasms should be documented. Moreover, a premalignant precursor, atypical endometriosis, has been reported to be frequently associated with cancer (9). However, there is still poor agreement on pathological criteria for its definition. Moreover, most cases lack histological evidence of merging between benign and malignant endometriosis since the endometriotic foci are obliterated by cancer overgrowth. Therefore, the exact frequency of endometriosis-related tumors is difficult to estimate.

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A pooled analysis of data from 13 case-control studies, including 7,911 women with invasive ovarian carcinoma and 13,226 controls, noted that endometriosis correlated with an increased risk of clear cell carcinoma (OR=3.05, 95% CI=2.43-3.84,  $p<0.0001$ ), low-grade serous carcinoma (HR=2.11, 95% CI=1.39-3.20,  $p<0.0001$ ) and endometrioid carcinoma (HR=2.04, 95% CI=1.67-2.48,  $p<0.0001$ ), whereas no association was found with high-grade serous carcinoma (10).

Ovarian endometrioid carcinoma harbors mutations of  $\beta$ -catenin encoding *CTNNB1* gene in 16-53% (11-13), phosphatase and tensin homolog (*PTEN*) gene in 14-21% (11-13) and AT-rich interactive domain 1A (*ARID1A*) gene in 30% of cases (14), respectively, whereas ovarian clear cell carcinoma displays mutations of phosphatidylinositol 3-kinase (*PIK3*) gene in 20-40% (12,15-17) and *ARID1A* gene in 15-61% (14, 15, 17-19) of the cases respectively, and frequent over-expression of hepatocyte nuclear factor-1beta (HNF-1b) (20, 21). An Italian preliminary study suggested that reduced expression of both hMLH1 and PTEN might be involved in the malignant evolution of endometriosis (22). *ARID1A* mutations have been detected in clear cell carcinomas and contiguous atypical endometriosis, but not in distant endometriotic lesions (14). Activation of PIK3-AKT-mTOR pathway, aberrant chromatin remodeling due to *ARID1A* mutation, and inactivation of estrogen receptor (ER) $\alpha$  signaling seem to play a major role in malignant transformation of ovarian endometriosis (12, 16-18, 23).

Deficient methylation of the ER $\beta$  promoter causes over-expression of ER $\beta$  in endometriotic stromal cells, which in turn suppresses ER $\alpha$  expression (24). A high ER $\beta$ -to-ER $\alpha$  ratio in endometriotic stromal cells results in both down-regulation of progesterone receptor (PR) and increased expression of cyclooxygenase (COX)-2, with consequent progesterone resistance and inflammation. Increased levels of cytokines and growth factors have been measured in the peritoneal fluid of women with endometriosis (25). Hyperestrogenism and inflammation may promote the growth and invasiveness of ectopic endometrium and constitute a link between endometriosis and ovarian cancer (26, 27). Moreover, the redox cycling of the great amount of free iron present in endometriotic cysts could lead to generation of reactive oxygen species (ROS), oxidative stress and DNA mutations that ultimately enhance carcinogenesis (28, 29). An immunohistochemical study found that the number of macrophages polarized as M2 phenotype and expressing heme oxygenase (HO)-1 was significantly decreased in tissue sections from 20 endometriosis-associated ovarian carcinomas compared to those from 33 benign ovarian endometriomas ( $p<0.001$ ) (30). HO-1 is an antioxidant enzyme involved in the resolution of inflammatory processes, but the molecular mechanisms by which reduced HO-1 expression promotes malignant transformation deserves further investigation.

There are no age-specific guidelines for the timing of active surveillance in asymptomatic women with ovarian endometrioma, which is usually removed when there is an atypical appearance or an enlarged size on imaging studies (31, 32). According to Song *et al.* (32) surveillance and counseling, with at least a 1-year interval, should be offered to these patients from the age of mid-thirties.

## Malignant Extraovarian Endometriosis

**General findings.** Approximately 18.3% to 25% of endometriosis-associated malignancies are extra-ovarian (5, 33-36). These neoplasias are usually endometrioid or clear cell carcinomas, whereas non-epithelial tumors are very rare and include endometrial stromal sarcomas (ESS)s, adenosarcomas, and carcinosarcomas (33, 36-38).

As far as the pathological diagnosis is concerned, the transition zone between benign and malignant endometriosis is detectable in only 36-42% of cases, and coexistence of a neoplasm and endometriotic tissue is sufficient to demonstrate the endometriotic origin of the lesion (Figure 1) (36, 37). Extra-ovarian malignancies can involve the colon and recto-vaginal septum, and more rarely, the small bowel, vulva, vagina, fallopian tube, urinary tract, pleura and pelvic lymph nodes, thus paralleling the distribution of benign extra-ovarian endometriosis (5, 25, 35, 36, 39-49). Scar endometriosis, *i.e.* the presence of functional endometrial tissue in surgical incisions, is a complication that can develop after obstetrical or gynecological surgical procedures (50). A few cases of endometriosis-associated malignancies in abdominal surgical or episiotomy scars have been reported in the literature (51-54).

Women with malignant extra-ovarian endometriosis are more likely to be postmenopausal, obese, and estrogen replacement therapy (ERT) users (3, 34-36, 39, 45, 55). Genetic anomalies, such as loss of heterozygosity on chromosome 5q, have also been noted (36).

In a retrospective study on archival tissue specimens, Lac *et al.* (56) detected somatic cancer-driver events in 11 of 40 (27.5%) cases of surgical scar endometriosis and 13 of 36 (36.1%) cases of deep infiltrating endometriosis, including hotspot mutations in *KRAS*, *ERBB2*, *PIK3CA* and *CTNNB1*. PTEN loss was observed at similar rates in both types of endometriosis (17.5% vs. 13.9%, respectively), whereas *ARID1A* loss occurred only in one case of deep infiltrating endometriosis. These alterations may be important for implantation and growth of endometriosis in these ectopic sites, whereas their role in carcinogenesis is still unknown. The prognosis of malignant extra-ovarian endometriosis is dependent on tumor stage, and 5-year survival ranges from 82% to 100% for patients with tumor confined to the site of origin and from 0% to 12% for those with disseminated intraperitoneal disease (3, 33, 34, 36).

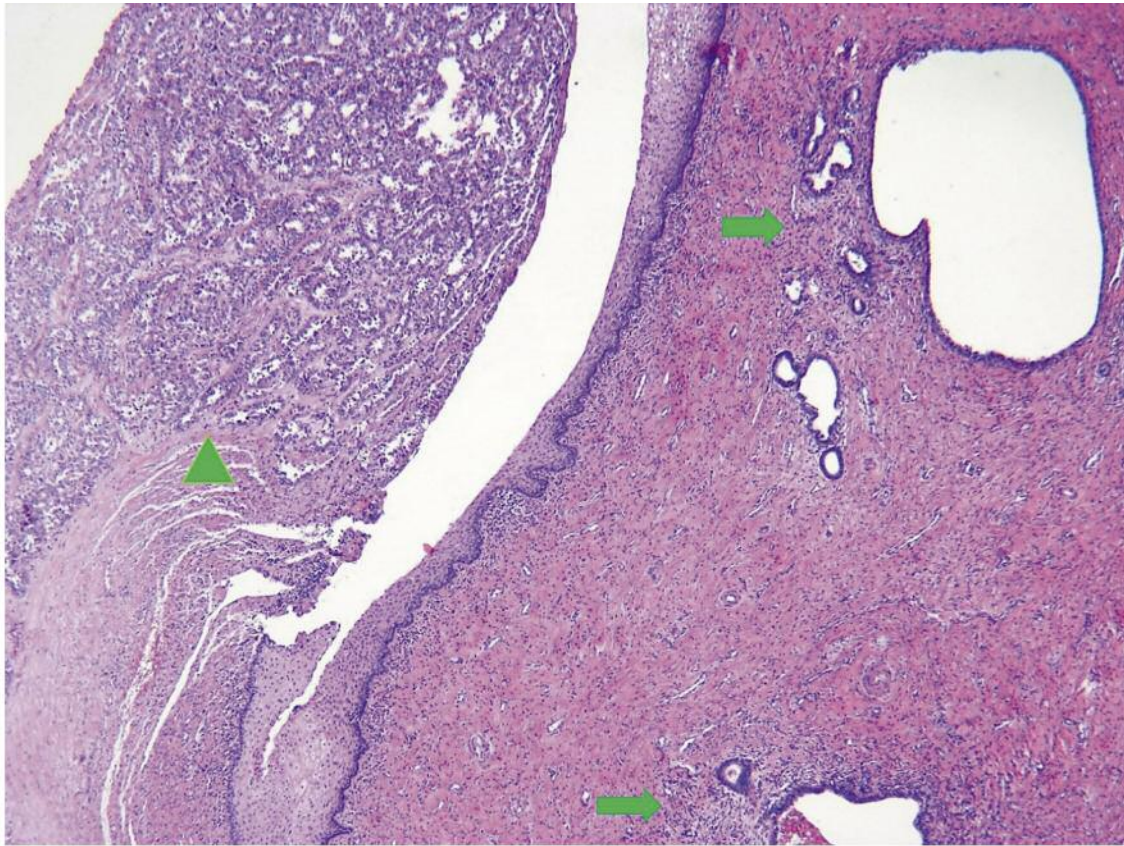


Figure 1. Haematoxylin and eosin (H&E) stained section, illustrating an example of endometrioid carcinoma (arrowhead) of the ureter, arising in association with endometriotic foci (arrows).

**Endometriosis-associated intestinal malignancies.** About 50 cases of endometriosis-associated intestinal tumors have been reported, and most were found in women in their mid-30s to early 50s (3, 35, 57-67). Sigmoid and colon-rectum have been involved up to 72% of cases, followed in frequency by small bowel, cecum and appendix. Marchena-Gomez *et al.* (68) described a metachronic malignant transformation of small bowel and rectal endometriosis in the same patient.

Symptoms and signs are similar to those of colon cancer, and include abdominal or pelvic pain, dyschezia, deep dyspareunia, hematochezia, rectorrhagia or melena, pelvic or abdominal mass, and less frequently, bowel occlusion or acute abdomen due to a mass, intussusception or perforation (3, 57, 60-62, 64, 65). Sometimes, the woman has a history of long-term cyclic intestinal symptoms labeled as irritable bowel syndrome (3). Molberg *et al.* (69) reported a case of endometrioid carcinoma arising in pericecal endometriosis that clinically and radiologically mimicked Crohn's disease.

Of the 40 women with endometriosis-associated intestinal cancers reviewed by Jones *et al.* (35), 17 patients had an

adenocarcinoma developing in the recto-sigmoid colon and 8 were using ERT. Kawate *et al.* (63) described the case of an endometrioid carcinoma of the mesocolon in a woman who underwent total hysterectomy and bilateral salpingo-oophorectomy for uterine fibroid and infiltrating pelvic endometriosis followed by ERT for 14 years.

Colonoscopy is useful to detect colorectal endometriosis, but when an adenocarcinoma is found at endoscopic examination the distinction between endometriosis-associated carcinoma and primary colon carcinoma may be difficult and the presence of surrounding benign endometriosis is warranted to support the diagnosis of endometrioid-related cancer (64, 66, 67).

Upon macroscopic examination, endometriosis-associated intestinal cancers develop in an extramural location and invade the bowel wall from the outside, thus involving the serosa and subserosa, and sometimes muscularis propria and submucosa, whereas the mucosa can be normal or shows minimal changes (3). Primary colon carcinomas display the opposite growth pattern, always involving bowel mucosa. At microscopic examination, the endometriotic origin of a

Table I. Immunohistochemistry for differential diagnosis between endometriosis- associated colon carcinoma and primary colon carcinoma.

	CK7	CK20	ER	CEA	VIMENTIN	CDX2
Endometriosis-associated colon carcinoma	+	–	+	–	+	–
Primary colon carcinoma	–	+	–	+	–	+

CK7, cytokeratin 7; CK20, cytokeratin 20; ER, estrogen receptor; CEA, carcino-embryonic antigen; CDX2, caudal-related homeobox transcription factor whose expression is normally restricted to intestinal epithelium.

tumor may be suggested by the presence of a squamous differentiation within a glandular neoplasm of the colon and by the detection of tubular glands with clean luminal contents and with the tumor cells lacking intracellular mucin and showing an alcian blue–positive glycocalyx (36, 58). A panel of immunohistochemical stains, including cytokeratin (CK) 7, CK 20, vimentin, carcinoembryonic antigen (CEA), CD10 and ER, may be useful for the differential diagnosis (3, 60, 61, 64-66, 70, 71) (Table I). Endometrioid glands are usually immunoreactive for CK7 and ER and stromal cells are positive for CD10 and ER, while intestinal glands express CDX2 and CK20 (66). Up to 80-100% of endometrioid carcinomas are CK7-positive and CK20-negative, whereas 75-95% of primary colonic carcinomas are CK7-negative and CK20-positive (71). The former are usually vimentin-positive and CEA-negative and the latter are commonly vimentin-negative and CEA-positive (60).

An immunohistochemical study showed a markedly decreased expression of N-cadherin in peritoneal and gastrointestinal endometriosis compared to proliferative endometrium, and a total lack of this cell surface protein, with preserved E-cadherin and beta-catenin expression, in endometriosis-associated intestinal cancers (72). Therefore, altered N-cadherin expression may be involved in the pathogenesis of gastrointestinal endometriosis and even in the development of malignancy.

Although there is no consensus on the therapeutic approach of these tumors, primary debulking surgery with resection of all macroscopic detectable lesions should be performed whenever possible (3, 59, 60, 62-64, 66-68, 73). Post-operative chemotherapy usually consists of carboplatin plus paclitaxel, although it obtains a poorer response compared to ovarian carcinoma (59, 64-66). The use of neoadjuvant chemotherapy in advanced cases as well as the administration of endocrine therapy in patients with ER+/PR+ tumors should be further investigated (65, 66, 73). Adjuvant radiotherapy has been sometimes given, especially in patients with limited pelvic involvement, but its real efficacy is still unknown (33, 65, 66, 73).

Kondo *et al.* (74) recently reported a case of long-term survival in a patient treated with chemotherapy only. The woman, who had previously undergone total hysterectomy and bilateral salpingo-oophorectomy for fibroids and

endometriosis and who had been taking ERT for 8 years, developed an endometrioid carcinoma involving the rectum, bladder, small bowel and vagina. She refused pelvic exenteration and underwent chemotherapy with carboplatin plus paclitaxel which obtained a complete response. Eleven years later the patient developed a vaginal recurrence which was surgically removed, with preservation of the bladder, rectum and small bowel, that was found to be a clear cell carcinoma associated with and that endometriosis.

Very few cases of ESSs arising from extra-gonadal endometriosis have been described in the literature (58, 75-78). Kim *et al.* (78) reviewed 16 extra-uterine and extra-ovarian ESSs, of which 8 involved the gastrointestinal tract, and found that these tumors had a higher tendency than their uterine counterparts to spread beyond the site of origin. Similarly to endometriosis-associated colon carcinomas, symptoms and signs consist of abdominal pain, bloating, rectal bleeding, palpable abdominal mass, stenosis of the recto-sigmoid colon or, less frequently, acute abdomen usually in postmenopausal women with or without a history of endometriosis (75-78). Mourra *et al.* (75) reported a case of ESS of the recto-sigmoid colon presenting with epigastric pain due to portal vein thrombosis in a 61-year-old woman who had no history of endometriosis and who had been receiving hormone replacement therapy for 13 years. She underwent recto-sigmoid colon resection with low anterior reanastomosis, did not receive any adjuvant treatment, and was alive with no evidence of disease after 30 months.

The differential diagnosis of ESSs of the gastrointestinal tract includes mesenchymal tumors, such as fibromatosis, schwannoma, and leiomyoma which present peculiar histological features, and gastrointestinal stromal tumors (GIST)s, characterized by a specific immunophenotype (75). GISTs show positive immunostaining for CD117 and CD34, and negative immunostaining for ER and PR, whereas ESSs are CD117-negative, CD34-negative, ER-positive and PR-positive (75, 78, 79) (Table II). Primary surgery with complete resection of all macroscopic disease should be attempted when feasible (75, 78, 80).

*Endometriosis-associated malignancies of the urinary tract.* Urinary tract endometriosis occurs in 1-5.5% of women with endometriosis, and the diagnosis may be difficult since this

Table II. *Immunohistochemistry for differential diagnosis between endometrial stromal sarcomas of the gastrointestinal tract and gastrointestinal stromal tumors.*

	CD117	CD34	ER	PR
ESS	–	–	+	+
GIST	+	+	–	–

CD117, Cluster of differentiation 117; CD34, cluster of differentiation 34; ER, estrogen receptor; PR, progesterone receptor; ESS, endometrial stromal sarcomas; GIST, gastrointestinal stromal tumors.

condition is often asymptomatic or associated with non-specific symptoms (81, 82).

To our knowledge, 11 cases of malignant transformation of endometriosis of the bladder have been reported in the literature (42-44, 48, 83-87). Seven tumors were clear cell carcinomas, 3 were endometrioid carcinomas, and one tumor was an adenosarcoma. At presentation symptoms included urinary frequency, incontinence and hematuria, suggesting the performance of urine cytology and cystoscopy with biopsies (43, 48, 84, 86). Sometimes the definite diagnosis emerged at histological examination of surgical specimens of transurethral resection of the bladder (48, 84).

These tumors were usually treated with radical cystectomy or exenteration with pelvic lymphadenectomy, often followed by platinum-based chemotherapy (single-agent carboplatin, carboplatin plus paclitaxel, or cisplatin plus epidoxorubicin plus paclitaxel) (43, 44, 48, 84-86). Adjuvant radiotherapy was sometimes delivered (86).

Four neoplasias arising from ureteral endometriosis have been described (49, 88-90). Histologically, 2 tumors were endometrioid carcinomas (Figure 1), one was an adenosquamous carcinoma and one was an endometrioid carcinoma with squamous differentiation. Three of these patients had undergone total hysterectomy and bilateral salpingo-oophorectomy followed by ERT for a period ranging from 5 to 14 years. At magnetic resonance (MR) or computed tomography (CT) scan the tumor appeared as a pelvic mass encasing the ureter, often associated with hydronephrosis. The patients were treated with ureterectomy and ureter anastomosis or nephro-ureterectomy, sometimes associated with pelvic and/or aortic-lymphadenectomy, omentectomy, and bowel resection, preceded and/or followed by chemotherapy consisting of carboplatin plus paclitaxel or cisplatin plus doxorubicin or carboplatin plus pegylated liposomal doxorubicin (49, 89, 90).

*Endometriosis-associated malignancies of surgical scars.* Endometriosis-associated malignancy in an abdominal surgical scar is a rare but aggressive phenomenon, with about 50 cases reported in the literature and with a median lag-time

from surgery of approximately 19 years (51, 52, 54, 91-110). These patients had previously undergone uterine surgery, mainly caesarean section and less frequently hysterectomy or myomectomy or surgery for uterine perforation. Macroscopically, the tumor appeared as a growing area of firmness closely related with midline abdominal hysterectomy scar or as a solid lower quadrant abdominal mass or as a fungating, ulcerated nodule with palpable subcutaneous extension associated with a cesarean section scar. The diagnosis was based on fine needle aspiration or biopsy of the lesion (52, 97, 105, 106, 108). Clear-cell carcinoma was the prevalent histological type (67%), followed by endometrioid carcinoma (15%), whereas only anecdotal cases of serous carcinoma or carcinosarcoma were described (51, 52, 54, 92-108, 110). A diagnostic curettage should be performed to rule out a primary endometrial carcinoma. The usual treatment consisted of an extensive resection of the abdominal wall with mesh or autologous skin-muscle graft reconstruction, preceded or followed by platinum-based chemotherapy (carboplatin plus paclitaxel, single agent- cisplatin or cisplatin plus cyclophosphamide) and sometimes by radiotherapy, although there is little evidence to support the benefit of these adjuvant treatments (51, 54, 92, 96-99, 101-110). Additional surgical procedures, such as hysterectomy, bilateral salpingo-oophorectomy and omentectomy, were sometimes performed. Omranipour and Najafi (106) treated a 59-year-old woman with a large size, serous carcinoma arising in abdominal wall endometriosis with 3 cycles of platinum-based neoadjuvant chemotherapy and debulking surgery followed by additional chemotherapy and radiotherapy. She was free of disease one year after surgery.

Five-year survival of patients with endometriosis-associated malignancy in an abdominal surgical scar is approximately 40%, with a median survival of 42 months and a tendency toward worse prognosis for clear cell histology and tumor diameter  $\geq 8$  cm in non-clear cell histology (54).

Six cases of malignant transformation of endometriosis in episiotomy scars have been described, with a lag-time from episiotomy ranging from a few months to over 40 years (53, 92, 111-114). The neoplasia appeared as an ulcerating lesion of the perineum and the buttock or as a soft, purple scar closely related to episiotomy. Histologically, 4 tumors were clear cell carcinomas, one tumor was a serous papillary carcinoma and one was an endometrioid carcinoma. The patients underwent radical vulvar excision sometimes with skin graft and groin lymphadenectomy, eventually preceded or followed by platinum-based chemotherapy and/or radiotherapy.

## Conclusion

Despite being considered a benign disease, endometriosis shares some features with cancer such as resistance to apoptosis and stimulation of angiogenesis (56). Genetic

variants of vascular endothelial growth factor (VEGF) may have a role in the development of endometriosis (115). The CC genotype of VEGF +405 and 460T/405C haplotypes of VEGF seem to be associated with an increased risk, whereas the G allele of VEGF +405 appears to be protective. The malignant transformation of endometriosis is an uncommon event, that, when occurring, it involves ovarian and extraovarian sites in 75% and 25% of cases, respectively. CTNNB1, PTEN, PIK3CA and ARID1A mutations are often detected in endometriosis-associated ovarian carcinomas, whereas few information is currently available on the molecular features of malignant extra-ovarian endometriosis. The latter can involve the bowel, and especially recto-sigmoid colon, and less frequently the urinary tract and surgical scars. The clinician should take into account the possibility of tumors arising from endometriosis when evaluating bowel or mesenteric neoplasms, even in a woman who has previously undergone total hysterectomy and bilateral salpingo-oophorectomy, especially if she has a history of quiescent endometriosis and has received ERT (63, 68). The distinction of a carcinoma arising from colonic endometriosis from a primary colonic carcinoma may be sometimes problematic, and immunohistochemistry is very useful for the differential diagnosis.

Only a few cases of endometriosis-associated malignancies in the urinary tract have been reported in the literature, and most of these involved the bladder. A systematic review of literature does not support the removal of bladder endometriotic lesions since their malignant transformation is exceedingly rare (87). On the other hand, some authors suggest that any scar lesion that modifies during the menstrual cycle should be considered endometriosis until proven otherwise, and thus it should require a surgical resection with histological examination or at least an accurate long-term follow-up (113).

According to a recent meta-analysis of 32 studies, women with endometriosis have an increased risk of endometrial cancer [summary relative risk (SRR)=1.38, 95% CI=1.10-1.74] and thyroid cancer (SRR=1.38, 95% CI=1.17-1.63), a decreased risk of cervical cancer (SRR=0.78, 95% CI=0.60-0.95), and an unchanged risk of breast cancer (SRR=1.04, 95% CI=0.99-1.09) and melanoma (SRR=1.31, 95% CI=0.86-1.96) (116). Further investigation is strongly warranted to elucidate the biological mechanisms underlying these associations.

## Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

## Authors' Contributions

Conceptualization, writing – original draft: AG; Data curation, formal analysis, methodology, writing-review & editing: AG, GF.

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