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The relationship of endometriosis and ovarian malignancy: a review

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Objective: To review the malignant potential of endometriosis based on epidemiologic, histopathologic, and molecular data.
Design: Literature review.
Result(s): The pathogenesis of endometriosis remains unclear. The histopathologic development of endometriosis has undergone long-term investigation. Studies have confirmed histologic transition from benign endometriosis to ovarian malignancy, including malignant transformation of extraovarian endometriosis. The prevalence of endometriosis in patients with epithelial ovarian cancer, especially in endometrioid and clear cell types, has been confirmed to be higher than in the general population. Ovarian cancers and adjacent endometriotic lesions have shown common genetic alterations, such as *PTEN*, *p53*, and *bcl* gene mutations, suggesting a possible malignant genetic transition spectrum. Furthermore, endometriosis has been associated with a chronic inflammatory state leading to cytokine release. These cytokines act in a complex system in which they induce or repress their own synthesis and can cause unregulated mitotic division, growth and differentiation, and migration or apoptosis similar to malignant mechanisms.
Conclusion(s): The malignant potential of endometriosis holds serious implications for management, such as the need for earlier and more meticulous surgical intervention for complete disease treatment. (Fertil Steril® 2008; 90:1559–70. ©2008 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, atypical endometriosis, malignant transformation, endometrioid carcinoma, clear cell carcinoma

Endometriosis has mixed traits of benign disease and malignancy. The pathogenesis involves loss of control of cell proliferation and is associated with local and distant spread; however, endometriosis does not cause catabolic disturbance, metabolic consequences, or death (1). Although endometriosis cannot be termed a premalignant condition, epidemiologic, histopathologic, and molecular data suggest that endometriosis does have malignant potential. Ovarian carcinogenesis may involve precursor lesions arising from endometriosis or those arising from mullerian metaplasia of the ovarian surface epithelium (OSE) as well as de novo carcinogenesis. This review addresses the parallels and specific relationship of endometriosis and ovarian cancer regarding risk factors, genetic alterations, aberrant activation of oncogenic and antiapoptotic pathways, and options in clinical diagnosis and therapy.

Theories on the histogenesis of endometriosis fall into five categories: celomic metaplasia, retrograde menstruation, embryonic cell rests, induction, and lymphatic and vascular dissemination (2–5). Ovarian carcinoma has been theorized to be caused by genetic alteration of damaged ovarian epithelium during ovulation, elevated gonadotropins, androgen excess with progesterone deficiency, retrograde menstruation with pelvic contamination with menstrual products, and chronic inflammation (6) (Table 1).

EPIDEMIOLOGY

The exact incidence of endometriosis is unknown, because accurate diagnosis requires surgical intervention and, even then, depends on the indication for surgery, type of procedure, and thoroughness and familiarity of the surgeon with different appearances of endometriosis. Approximately

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TABLE 1

An overview of common factors of both endometriosis and ovarian cancer.

Similar theories on etiology	Protective factors	Risk factors	Common pathogenetic mechanisms
■ Damaged ovarian epithelium ■ Elevated gonadotropins ■ Androgen excess with progesterone deficiency ■ Retrograde menstruation ■ Chronic inflammation	■ Oral contraceptives ■ Tubal ligation ■ Hysterectomy ■ Pregnancy	■ Early menarche ■ Late menopause	■ Familial predisposition ■ Immunobiological factors ■ Cell adhesion factors ■ Angiogenic factors

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3%–10% of reproductive-age women, 25%–80 % of infertile women, 2%–5% of postmenopausal women, and 40%–80% of women with pelvic pain are afflicted with endometriosis. The specific correlation of endometriosis and ovarian malignancy and their epidemiologic patterns have been extensively studied. There is suggestion of a common mechanism based on similar disease responses, such as the protective effects of tubal ligation, hysterectomy, oral contraceptives, and pregnancy, increased risks with infertility, and early menarche, late menopause, and nulliparity for both ovarian cancer and endometriosis (6) (Table 1).

The prevalence of ovarian cancer developing in women with endometriosis is higher than sporadic ovarian cancer in the general population. Several studies have specifically addressed the ovarian cancer risk in patients with endometriosis. Brinton et al. (7) reviewed 20,686 women hospitalized with endometriosis identified through the Swedish Inpatient Registry from 1969 to 1983 with a mean follow-up of 11.4 years. The cases of all incident cancers in this cohort were garnered through the National Swedish Cancer Registry, identifying 738 overall malignancies and 29 ovarian malignancies. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) from this study showed an increased overall cancer risk of 1.2 (1.1–1.3), 1.9 (1.3–2.8) for ovarian cancer, 1.3 (1.1–1.4) for breast cancer, and 1.8 (1.0–1.8) for hematopoetic cancers. The incidence ratio for those with follow-up of ≥ 10 years increased to 2.5, and the highest cancer risk was among women with the longest history of endometriosis: SIR 4.2 (95% CI 2.0–7.7). This analysis may overestimate the cancer risk, because only hospitalized endometriosis patients were accounted for. Borgfeldt and Andolf (8) also identified a cohort of 28,163 endometriosis patients born before 1970 from the National Swedish Hospital Discharge Registry from 1969 to 1996 and matched each case with three controls. The cohort of endometriosis patients had an increased risk for ovarian cancer of 1.3 (95% CI 1.0–1.8) with a significantly lower mean age at diagnosis of 49 years versus 51.6 years in control population.

The significance of this relationship was further confirmed by Brinton et al. in 2004 (9) with a retrospective cohort study conducted in the United States, analyzing the correlation of endometriosis causing primary infertility and ovarian cancer, resulting in an SIR of 4.19 (95% CI 2.0–7.7) and a risk ratio of 2.72 (95% CI 1.1–6.7) compared with patients with secondary infertility and no endometriosis. Further analysis within the cohort of primary infertility patients with endometriosis in 2005 by Brinton et al. (10) again revealed elevated relative risks (95% CI) of 2.9 (1.2–7.1) for ovarian cancer, 2.4 (0.7–8.4) for colon cancer, 4.65 (0.8–25.6) for thyroid cancer, and 2.3 (0.8–6.7) for melanomas. These Swedish cohort studies were expanded by Melin et al. in 2006 (11) to evaluate if risk ratios were consistent with longer follow-up. The cohort was 64,492 endometriosis patients discharged from hospitalization identified through the Swedish Inpatient Registry from 1969 to 2000. When cross-referenced with the National Swedish Cancer Registry, 3,349 patients were identified to have developed ovarian cancer. With extended follow-up and calculation of updated standardized incidence ratios, there was no risk for overall cancer (1.04), but an increase was noted in ovarian cancer (1.43 [95% CI 1.2–1.7]), endocrine tumors (1.36 [95% CI 1.2–1.6]), non-Hodgkin lymphoma (1.24 [95% CI 1.0–1.50]), and brain tumors (1.22 [95% CI 1.0–1.4]). Again, risk for women with early diagnosis and long-standing endometriosis was most pronounced, with SIRs of 2.01 and 2.23, respectively. Of note, women with a history of hysterectomy at or before time of endometriosis diagnosis did not show an elevated risk (11). Again, both studies of the Swedish cohorts may be skewed to reflect malignant incidence ratios for cases of more severe endometriosis, because the cohorts were hospitalized patients with more advanced stages of endometriosis. Also, because records of hospitalized patients were retrospectively cross-referenced with a separate cancer patient registry, there is the possibility of negating or including cases erroneously.

The most recent study from Japan followed a cohort of 6,398 women with clinically documented endometriomas and evaluated the risk of ovarian cancer based on varying time periods from time of diagnosis of endometriosis (12). During follow-up of up to 17 years, 46 incidental ovarian cancers were identified, translating into a standardized incidence ratio of 8.95. This risk increased with age, with an incidence ratio of 13.2 in women over age 50 (12). Of note, only approximately one-third of these patients had surgically

confirmed endometriomas, with the remaining diagnoses made based on ultrasonographic findings and physical exam only. Furthermore, this study did not account for patients with extraovarian endometriosis.

Olsen et al. (13) completed the largest study that did not support the increased ovarian cancer risk in endometriosis patients. Analyzing a group of 37,434 postmenopausal women, a cohort of 1,392 postmenopausal patients who self-reported the diagnosis of endometriosis was isolated. After an average 13-year follow-up, no significant increased risk was found for all cancers, breast cancer, or ovarian cancer, but there was a significant association with increased risk of non-Hodgkin lymphoma, with an age-adjusted risk ratio of 1.8 (95% CI 1.0–3.0). This study involved acceptable long-term follow-up; however, several factors must be taken into account. The cohort was smaller, with only three ovarian cancer cases, making it underpowered. Furthermore, the endometriosis was not medically confirmed and, because all of the patients were postmenopausal, it is possible that younger patients may have already developed ovarian cancer and died. Table 2 summarizes the epidemiologic studies of ovarian cancer risk in endometriosis patients.

Reciprocal analysis of the prevalence of endometriosis found in ovarian cancer patients also supports the correlation. In a review of 29 studies from 1973 to 2002 on the prevalence of endometriosis in epithelial ovarian cancers organized by location of disease, the following three groups were compiled: histologic proof of transition from ovarian endometriosis to cancer as defined by Sampson (5), ovarian cancers with endometriosis in the same ovary, and ovarian cancers with concomitant pelvic endometriosis. The second category was considered to be the best estimation of endometriosis in the different histologic subtypes, yielding a prevalence of 4.5% in serous, 1.4% in mucinous, 35.9% in clear-cell, and 19% in endometrioid carcinomas (6).

These data were further corroborated by Valenzuela et al. in 2007 (14); among 22 cases of ovarian endometrioid adenocarcinomas of the ovary, three patients were found to have concomitant endometriosis as defined by the Sampson criteria. The review by Van Gorp et al. (6) calculated an ovarian cancer prevalence of 0.9% in all cases of endometriosis, 2.5% when present in the same ovary, and 4.5% when coexistent with any pelvic endometriosis. Malignant extraovarian endometriosis is estimated to account for 25% of all malignant transformations of endometriosis and 80% of the endometrioid subtype (15–17).

Overall, looking at the trend of ovarian cancer in endometriosis is more difficult, because endometriosis is not always as aggressively resected and confirmed by pathologic studies. Only a limited number of the studies controlled for confounding factors for both diseases, such as parity, infertility, tubal ligation, ovarian hyperstimulation, and duration of endometriosis. Ness et al. (18) completed two case-control studies confirming the association between endometriosis and ovarian cancer. In a group of 767 women with ovarian cancer and 1,367 control subjects, with adjustments made for age, parity, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding, overall women with breast cancer were 1.7-fold more likely to report an endometriosis history (18). Furthermore, in a pooled study of 13,000 women, ovarian cancer was more likely among subfertile women, especially with infertility resulting from endometriosis, showing an odds ratio of 1.9 (95% CI 1.2–2.9) (19).

The relationship of endometriosis and ovarian cancer was further explored in terms of bias versus causality using the nine criteria proposed by Austin Bradford Hill which serve as fundamentals of causal inference: strength of association, consistency, biologic gradient, specificity, temporality, biologic plausibility, experimental evidence, analogy, and coherence (20). The criterion of strength was not fulfilled, and data on the association was insufficient or mixed for biologic gradient, plausibility, analogy, and coherence. However, fulfilled criteria were consistency, temporality, specificity, and experimental evidence in animal models. The article concluded that a causal relationship between endometriosis and ovarian cancer should be recognized, but that the low degree of risk observed could be attributed to the possibility that ectopic and eutopic endometrium undergo malignant transformation at similar rates (20).

MOLECULAR PATHOGENESIS

Common pathogenetic factors of both endometriosis and ovarian malignancy include familial predisposition, genetic alterations, immunobiologic, cell adhesion, angiogenic, and hormonal factors (Table 1).

Genomic Instability and Mutations

Although there are reports of mendelian inheritance patterns of endometriosis, such as an increased risk in first-degree relatives and twins, there is increasing evidence that endometriosis is inherited as a complex genetic trait involving the interaction of multiple genes and environmental factors conferring disease susceptibility and malignant behaviors (21).

Genomic instability is a known characteristic of cancer cells. Endometriosis demonstrates somatically acquired genetic alterations similar to those found in cancer, leading to clonal expansion of genetically abnormal cells, as demonstrated in several studies (22, 23). Endometriotic cysts are monoclonal and characterized by the loss of heterozygosity in 75% of endometriotic cyst cases with associated adenocarcimona, and even in 28% of cases without accompanying carcinoma. The most commonly affected chromosome arms are 9p, 11q, and 22q (24). Comparative genomic hybridization studies of endometriosis have revealed loss of DNA copy numbers on 1p, 22q, and X, and gain on 6p and 17q. Fluorescent in situ hybridization analyses confirmed that gain of 17q includes amplification of the proto-oncogene *HER-2/neu* (25). Loss of heterozygosity at 5q, 6q, 9p, 11q, 22q, p16, and p53, indicating loss of tumor suppression genes, has

studies assessing ovarian cancer risk in endometriosis patients.

Study Type	Cohort Size	Mean Follow Up (Years)	Ovarian Malignancies Identified	Ovarian cancer in endometriosis patients SIR/OR	
Cohort	20, 686 endometriosis patients	11.4	29	Overall cancer risk	1.2
				Ovarian cancer	1.9
				Ovarian cancer with ≥10 yrs followup	2.5
				Ovarian cancer with Longstanding endometriosis	4.2
Cohort	12,193 infertility patients		45	Ovarian cancer	2.5
Cohort			2,491	2.53 (1.19-5.38)	
Case control			66	Ovarian cancer	1.7
Nested case control	28,163		81	Ovarian cancer	1.3
Case control			177	1.3 (1.1-1.6)	
Cohort	64,492	12.7	122	Overall cancer risk	1.04
				Ovarian cancer	1.43
				Ovarian cancer Early diagnosed endometriosis	2.0
				Ovarian cancer Long standing endometriosis	2.2
Cohort	1,392	13	3	No increased risk for overall or ovarian cancer	
Cohort	6,398	12.8	46	Ovarian cancer	8.95
				Ovarian cancer > 50 yrs old	13.2

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been identified in endometriosis and endometriosis-derived cell lines (26). Ovarian cancers and adjacent endometriotic lesions have shown common genetic alterations, such as *PTEN* gene mutations, suggesting a possible malignant genetic transition spectrum. Loss of heterogenicity at 10q23.3 occurs with high frequency in solitary endometrial cysts (56.5%), endometrioid carcinoma of the ovary (42.1%), and clear cell carcinoma of the ovary (27.3%), and a concentration of mutations in the *PTEN* gene encoding the phosphatase domain has been demonstrated in endometrial cysts and clear cell carcinomas of the ovary (27). In a mouse model of endometrioid ovarian cancer, *PTEN* deletion in the background of oncogenic *K-ras* activation within the OSE gives rise to endometriotic-like precursor lesions which developed invasive endometrioid ovarian carcinoma within 7–12 weeks (28). These studies demonstrate that benign endometriosis-like lesions can develop within the normal OSE after expression of oncogenic *K-ras*; however, progression to endometrioid ovarian cancer necessitates inactivation of *PTEN*. Additional data provided by Dinulescu et al. (28) show activation of PI3K (phosphatydylinositol 3′ kinase)-AKT-mTOR (mammalian target of rapamycin) and MAP kinase pathways in this model, suggesting potential utility of the model in therapeutic protocols. Based on these data, Matzuk (29) proposed that activation of β-catenin may be involved in endometrioid or clear cell carcinoma of the ovary. Several lines of investigation exploring the genetic modifications of mouse ovarian surface epithelial cells necessary for tumorigenic transformation delineate that inactivation of p53 and activation of *c-myc*, *K-ras*, or *AKT* contribute to early tumorigenesis (30). Cheng et al. (31) demonstrated in an explant model of epithelial ovarian cancer that aberrant *Hoxa10* expression along with *Hoxa7* and *Hoxa9* confer early endometrioid differentiation. The authors speculated that deregulated expression of *HOX* genes " tip the balance toward tumorigenicity" in "phenotypically uncommitted" OSE undergoing neoplastic transformation.

Abnormal gene expression of the tumor suppression gene *PTEN* and DNA mismatch repair gene *hMLH1* was identified in endometrial and ovarian cancers and has been similarly recognized in advanced-stage endometriosis. A 2002 study by Martini et al. (32) analyzed the methylation status of *hMLH1* and *p16* and the protein expression of *PTEN* and *hMLH1* in 46 cases of endometriosis stages III and IV. Hypermethylation resulting in absence of the hMLH1 protein was noted in 8.6% of endometriotic lesions, and reduced protein expression of PTEN was noted in 15% of cases (32). Frequent mutations of the *PTEN* gene are seen in endometrioid ovarian tumor compared with eutopic endometrium counterparts, but not in serous or mucinous epithelial ovarian tumors. (33). Overexpression of p53 and bcl-2 proteins involved in apoptosis and matrix metalloproteinase 9 involved in basement membrane dissolution has been reported in cancers and associated endometriosis compared with benign control samples (34, 35).

Transitional Phenotype

In the background of endometriosis, malignant progression at the ovary to endometrioid and clear cell carcinoma after severe atypia is a biologically plausible phenomenon of multidimensional molecular complexity. Malignant transformation of endometriosis was first reported by Sampson (5) with the following criteria: 1) coexistence of carcinoma and endometriosis of the same ovary; 2) a similar histologic relationship; and 3) exclusion of another primary site. Later, Scott (36) added that benign endometriosis should be contiguous with malignant tissue, but this has rarely been found, owing to sampling technique and possible destruction of benign tissue by tumor invasion. However, studies have confirmed histologic transition from endometriosis in direct continuity with tumor and malignant transformation of extraovarian endometriosis and cytologically "atypical" endometriosis. About 60%–80% of cases of endometrioid endometriosis-associated ovarian cancers (EAOCs) arise in the presence of atypical endometriosis. Of these cases, 25% show direct continuity with the atypical ovarian endometriosis (37, 38). Okamura and Katabuchi (39, 40) presented evidence of direct transition from endometriotic gland to atypia to carcinoma in endometrioid carcinoma arising from an ovarian endometriotic cyst.

In more extensive studies of up to 1,000 cases, ovarian cancer was present in 5%–10% of ovarian endometriotic lesions (41). Regarding the exact histology of the tumors, ovarian cancers associated with endometriosis were up to 60% endometrioid and up to 15% clear cell, proportions much greater than the general make-up of the ovarian cancer population. Inversely, 40% of 79 women with stage I ovarian cancer had associated endometriosis: 41% of the cases were endometrioid, 31% clear cell, and 18% mixed endometrioid–clear cell. Out of the 22 cancer patients with endometriosis, seven (32%) had discernible tumors arising directly out of endometriosis lesions. This histologic pattern was corroborated with a combination of clinical and histologic data by Deligdisch et al. (42) of 76 International Federation of Gynecology and Obstetrics stage I ovarian carcinomas, 54 cases (71%) were nonserous types (endometrioid and clear cell) and 22 (29%) were serous pathology. Ovarian endometriosis was present in 40 of the 76 cases, of which 39 were nonserous carcinomas. Several studies support the pathologic malignant transition of endometriosis in about 5%–10% of women found to have ovarian endometriomas at surgery versus 1.5% in the general population. Moll et al. (43) reported the occurrence of clear cell carcinoma in a patient with atypia in the presence of endometriosis within 3 years.

Biologic Modulators

The implantation of ectopic endometriosis on OSE generates a distinct microenvironment in which regulatory signals from multiple cell types affect signaling pathways and integrated circuits of each cell type, changing the physiologic homeostasis under which these cells function in normalcy. The principal biologic modulators localized within this microenvironment are growth factors inducing proliferation, cytokines promoting cell activation and proliferation, hormones inducing nuclear factors and inflammatory mediators, and

chemokines inducing chemotaxis and cell migration. Based on existing observations it is increasingly evident that within the endometriosis–ovarian cancer entity, these molecular mediators, along with genetic factors, confer cellular capabilities toward the acquisition of a malignant phenotype. The features of the malignant phenotype were recently outlined by the landmark publication of Hanahan and Weinberg on the hallmarks of cancer (44). Accordingly, a cancer cell must have self-sufficiency in growth signals, insensitivity to antiproliferative signals, resistance to apoptosis, sustained angiogenesis, tissue invasion and metastasis, and genomic instability. Green and Evan theorized that "deregulation of proliferation, together with a reduction of apoptosis, creates a platform that is both necessary and sufficient for cancer" (45). The subsequent molecular aberrations of endometriosis may explain the possibility of malignant transformation at the ovarian endometriosis foci within this context. Furthermore, it is widely accepted that the OSE harbors pleuripotential embryonic properties, including a capacity to undergo an epithelial-mesenchymal conversion as well as differentiation along the mullerian duct pathway, with characteristics of metaplasia (46).

Cheng et al. (31) offered a molecular explanation for the emergence of mullerian differentiation in ovarian cancer, including expression of epithelial membrane antigens such as mucins and E-cadherin, attributable to the expression of specific combinations of the homeobox genes. The mucin MUC1, used frequently as a marker for preneoplastic lesions and many chronic inflammatory diseases, is present in ovarian endometriosis and is overexpressed and deficiently glycosylated in endometrioid and clear cell carcinoma as well as other ovarian tumors (47). Expression of E-cadherin emerges in OSE of inclusion cysts and may render OSE cells more susceptible to neoplastic transformation (46). The frequency of mullerian differentiation may be a factor in initiation of transformation of the OSE (48); however, molecular aberrations characteristic for inflammatory processes in endometriosis may contribute with a number of survival and growth signals toward malignant transformation of OSE. Furthermore, several cytokines are expressed in the normal ovary, and their levels are fine-tuned to regulate physiologic functions such as follicular development. Endometriosis at the ovary confers an imbalance in the cytokine milieu, inducing surges of immunomodulatory and growth-stimulating cytokines similar to those observed in ovarian malignancy. In addition, endometriosis drastically changes the hormonal milieu at the ovarian epithelial surface. Thus, endometriosis generates growth signals to which ovarian cancer cells have demonstrated dependency. In theory, the propensity of endometriotic cells to expand clonally, as a result of intrinsic anomalities and advanced inflammation in endometriosis, generates a constitutive abundant flux of several stimulatory signals which OSE cells persistently exploit, resulting in the induction of progressive transcriptional changes that drive sustained proliferation, increasing the rate of DNA repair and the likelihood of accumulation of mutations in these cells.

As noted for centuries, inflammation may be central to tumorigenesis. Balkwill and Mantovany offer an elegant description of this link: "If genetic damage is the 'match that lights a fire' of cancer, some types of inflammation may provide 'the fuel that feeds the flames'" (49). Inflammation is considered to be a hallmark of endometriosis, with local and systemic implications (50). Local inflammatory reactions at the endometriotic implant site elicit proinflamatory protein secretion by associated immune cells as well as cells integral to the implant. The orchestrated aberrant expression of proinflammatory IL-1, IL-6, IL-8, and TNF-α alter several physiologic processes leading to cell survival at the endometriosis-ovarian junction. Chronically activated innate immune cells within this microenvironment can regulate intracellular signaling pathways through nuclear factor (NF) κB, thus directly promoting transformation via paracrine modulation. Indirectly, chronically activated innate immune cells suppress antitumor adaptive immune responses. The central role of NF-κB and its activating kinases IKKα and IKKβ in linking cancer to inflammation by differential regulation of cell survival and production of proinflammatory cytokines has recently been established (51, 52). In the subsequent sections we discuss the use of the proinflammatory interleukin (IL) 1, IL-6, and transforming growth factor (TGF) β, tumor necrosis factor (TNF) α, the chemokine IL-8, hormones, and growth factors within the endometriosis-ovarian microenvironment:

Interleukin-1 High concentrations of IL-1, produced by macrophages, are found in the peritoneal fluid of women with endometriosis (53). Interleukin-1β can up-regulate COX-2 promoter activity in ectopic endometriotic tissue, and, compared with eutopic endometrium, ectopic endometriotic implants from patients with ovarian endometrioma show much higher COX-2 mRNA, possibly contributing to sustained elevation of COX-2 and concomitant prostaglandin-E_2 production. This induction of COX-2 expression by IL-1β in ectopic implants is 100 times more sensitive compared with eutopic loci (54). COX-2 is up-regulated in several cancers and premalignant conditions, and it is thought to contribute to tumor cell proliferation, survival and angiogenesis. In the ovary, COX-2 is implicated in early events of neoplastic transformation, because it is rarely found in normal OSE but is present in ovarian inclusion cysts (considered to be premalignant). Furthermore, expression levels of COX-2 increase progressively in malignant ovarian tumors (55). Microarray analysis of cultured ovarian epithelium shows that IL-1 can up-regulate the steroidogenic gene expressing 11β-HSD-1 and suppress the GnRH receptor, thus inducing glycocorticoids and progesterone irresponsiveness, respectively, which may trigger proliferation (56).

Interleukin-8 Interleukin-8 is a proinflammatory chemokine unique to humans. It is a macrophage-derived protein that triggers rapid migration of neutrophils. Ectopic endometrial cells express high concentrations of IL-8 (57). Peritoneal fluid of women with endometriosis contains high concentrations of IL-8, derived largely from peritoneal macrophages

(58). Although peripheral blood concentrations of IL-8 are not related to the presence of endometriosis, this cytokine shows increased levels in the cyst fluid of endometriomas and ovarian carcinomas, with highest concentrations observed in the fluid of malignant ovarian cysts (59). It has been demonstrated that activation of the *ras* proto-oncogene can up-regulate IL-8, resulting in inflammatory activity at tumor sites, vasculogenesis, and tumor growth (60). Further, IL-8 has been shown to increase soluble Fas ligand in endometriotic lesions, thus inducing apoptosis of T cells relevant to immune-mediated cell death, consequently increasing the chance of malignant cells to evade immune surveillance within the ovarian endometriosis foci (61).

TNF-α Tumor necrosis factor α is produced by peritoneal macrophages and endometriotic lesions. It has been shown to promote endometrial cell proliferation, adhesion, and angiogenesis. Concentrations of TNF–α are elevated in the serum of women with endometriomas and those with ovarian malignancy. The TNF-α levels are increased in the fluid of malignant ovarian cysts compared with endometriomas and benign ovarian tumors, the latter two having similar levels of TNF-α in their cyst fluid (59). Recent studies underpin the importance of the TNF-α/IKKβ signaling pathway in linking inflammation to cancer by inducing evasion of apoptosis and insensitivity of antigrowth signals (52). Tumor necrosis factor α is implicated in the promotion and progression of premalignant cells by activation of the NF-κB–dependent antiapoptotic pathway in magnitude and duration. In vitro studies by Kulbe et al. (62) show that TNF-α, produced in an autocrine fashion by ovarian cancer cell lines, leads to the stimulation, among others, of the angiogenic vascular endothelial growth factor (VEGF), the cytokine IL-6, the chemokine CCL2, and the chemokine CXCL12. These mediators form a close network of interactions, where TNF-α acts as an inducer of VEGF and VEGF as an inducer of the chemokine CXCL12, all contributing to stimulation of neovascularization in ovarian cancer. Moreover, stimulation of ovarian epithelial cells and ovarian cancer cell lines with TNF-α leads to the up-regulation of CXCR4, the receptor for CXCL12. The expression of the chemokine receptor CXCR4 is thought to increase survival and metastatic potential of epithelial ovarian cells via NF-κB, resulting in increased proliferation under suboptimal conditions (62). Clearly, ovarian cancer cells are dependent on a constitutive network of tumor-promoting cytokines and angiogenic factors sustained by TNF-α. Within the endometriosis-ovarian microenvironment, high TNF-α levels could be maintained by the endometriotic implant, thus promoting growth activity in OSE cells.

Furthermore, TNF-α differentially modulates the expression of adhesion molecule CD44 in ovarian cancer cells in vitro (63). It is of interest that the CD44s isoform is found expressed in 86% of ovarian clear cell carcinoma, but only in 9% of ovarian endometrioid carcinoma (64). CD44 is a membrane receptor, with many isoforms playing differential roles in cell proliferation, adhesion, motility, and metastasis via the PAK1 signaling pathway. CD44 is found associated with HER2/neu in ovarian cancer cells, and signaling derived through this association is considered to be important in the development of ovarian malignancies (65). HER2/neu is overexpressed in most ovarian cancers (66).

Inflammation-mediated tumor angiogenesis in cultured breast cancer cells in response to TNF-α is achieved through VEGF up-regulation, via a recently delineated novel pathway based on deregulation of mTOR signaling, where the suppression of the tumor suppressor TSC1 by IKKβ, an inflammation-associated kinase, leads to mTOR activation (52). The involvement of mTOR in inflammation-mediated tumor progression promises novel potential antiangiogenic therapy. Clearly, inflammatory mediators such as TNF-α can up-regulate VEGF; however, VEGF in itself is shown to affect the inflammatory process by inducing peripheral blood mononuclear cells to produce increased levels of TNF-α and IL-6, as well as by augmenting the T_H1 phenotype leading to an increase in IL-2 and interferon (IFN) γ (67). The peritoneal fluid of patients with endometriosis contains increased VEGF concentrations compared with normal subjects (68), consistent with the finding that peritoneal T cells of women with endometriosis express predominantly IL-2 and IFN-γ. The VEGF concentrations are also elevated in endometriotic tissue (69).

TGF-β The peritoneal fluid of women with endometriosis shows increased TGF-β activity as well, and women with a higher stage of endometriosis exhibit a higher concentration of TGF-β in their peritoneal fluid (70). Transforming growth factor β is implicated in ovarian tumorigenesis. Normal OSE cells are responsive to growth inhibitory effects of TGF-β via down-regulation of c-myc, although ovarian cancer cells lose their responsiveness to TGF-β. Resistance to TGF-β in these cells coincides with loss of c-myc down-regulation in the presence of functional classic TGF-β signaling pathway. It has been suggested that ovarian cancer cells acquire selective advantage by expressing a functional tumor-promoting TGF-β signaling pathway leading to angiogenesis and immune suppression, and the loss of c-myc down-regulation triggers repression of antiproliferative responses via p15 INK4β (71). Thus, signaling through TGF-β disrupts antiproliferative circuits.

Interleukin-6 Inflammation-mediated activation of the transcription factor NF-κB in myeloid cells within the endometriosis-ovarian-junction microenvironment leads to up-regulation of many proinflammatory cytokines, including IL-6. Interleukin-6 is secreted by endometriotic peritoneal macrophages as well as ectopic implant cells (72). Interleukin-6 is secreted by endometriotic cells together with IFN-γ and may up-regulate soluble intracellular adhesion molecule (ICAM) 1 production by macrophages in patients with endometriosis. Expression of soluble ICAM-1 is also up-regulated in ectopic endometrium compared with eutopic endometrium (73), and soluble ICAM-1 levels are increased in the peritoneum of women with endometriosis (74). High

concentrations of soluble ICAM-1 may affect the function of immune cells involved in tumor surveillance by blocking the interaction of lymphocyte function-associated antigen (LFA) 1–positive immune cells with ICAM-1–expressing target cells, resulting in impaired immune response, thus enabling malignant cells to evade immune surveillance. An increase of serum levels of IL-6 is noted in women with endometriomas as well as women with malignant ovarian cancer; however, the levels of this cytokine are similar in endometriotic cyst fluid compared with malignant and benign ovarian tumors (59).

Endocrine factors Both endometriotic cell components and ovarian surface epithelium have the capacity to undergo proliferation in response to endocrine and growth factors. In that respect an important aberration of ectopic endometrial cells, namely, the pathologic expression of P450 aromatase, triggers constitutive expression of E_2 (75). A second anomaly of this tissue is the lack of the enzyme 17β-HSD-2, which converts E_2 to estrone, leading to further accumulation of E_2. Elevated estrogen levels stimulate COX-2 production in these cells, leading to an increase of prostaglandin-E_2 production, which in turn stimulates further aromatase activity contributing to the constitutive production of E_2. Prostaglandin-E_2 is itself implicated in tumor progression, and ovarian tumors are shown to contain increased levels of this prostaglandin (76). Additionally, ectopic endometriotic cells express low levels of the progesterone receptor isoform A and none of isoform B, rendering these cells unresponsive to progesterone and prone to proliferation, thus increasing levels of E_2 in the microenvironment (76). Further proliferation may be promulgated, because E_2 can stimulate cytokine production, in particular, IL-8 and RANTES (77). A marked reduction in expression of the two progesterone receptor isoforms is also noted in ovarian carcinoma specimens, leading to unresponsiveness of those cells to progesterone and thus increasing the possibility for proliferation (78, 79). The estrogen-rich environment created by endometriotic cells may also trigger increased responsiveness to E_2 in malignant ovarian epithelia via altered expression of estrogen receptors in those cells (80), thus further promulgating growth of malignant cells. Estradiol is also shown to regulate the production of IL-6 in malignant human OSE cells, promoting growth of these cells in an autocrine fashion (81). Importantly, in vitro studies of immortalized OSE cells demonstrate estrogen-mediated up-regulation of hTERT via direct and indirect stimulation of the hTERT promoter, enabling these cells to achieve malignancy (82). Clearly, high estrogen levels persist in the microenvironment created by the presence of an endometriotic implant at the ovary, generating a highly altered physiologic milieu surrounding the OSE, which suggests proliferative pressure with enhanced level of reparative activity, and thus a higher chance of DNA damage and mutations. Specific changes in hormone receptors and enzyme expressions in transformed OSE cells continually exposed to nonphysiologic hormonal conditions may lead to further progression to malignancy.

Growth factors Increased estrogen levels associated with the proximity of endometriotic cells may trigger up-regulation of insulin-like growth factor (IGF)–binding proteins in OSE cells, leading to estrogen-induced growth (83). Moreover, IGF-1 signaling in these cells may be altered by the higher levels of plasma IGF-1 shown in severe cases of endometriosis (84) and the higher levels of IGF-1 in the peritoneal fluid of women with endometriosis (85). Up-regulation of IGF-1 has been shown to inhibit apoptosis in normal human OSE cells after hCG exposure (86). Thus, in the presence of endometriosis, dysregulation of IGF-1–mediated signaling also may be a potential factor in the induction of proliferative activity of OSE.

In addition to IGF-1, the peritoneal fluid of women with endometriosis contains significantly higher levels of several other growth factors compared with patients without endometriosis. In severe endometriosis, high levels of hepatocyte growth factor (HGF) in the peritoneal fluid have been observed (87). During normal OSE development, a paracrine interaction between HGF and its receptor, Met, is necessary in ovarian physiology; however, this balance is perturbed in ovarian cancer cells, and the generation of an autocrine HGF-Met loop confers malignant transformation of the OSE. High peritoneal levels of HGF in the presence of endometriosis may trigger similar imbalance, resulting in mitogenic activity of OSE. This is supported by the fact that high levels of HGF are also present in the fluid of malignant ovarian cysts compared with benign cysts (88) and that Met is expressed in high levels in 28% of epithelial ovarian cancer and levels of expression increase in differentiated ovarian carcinomas compared with normal OSE (89, 90). In addition, in patients with hereditary ovarian cancer, enhanced stability of c-Met and HGF secretion are implicated as early factors in ovarian carcinogenesis (91). Platelet-derived growth factor also has been identified in the peritoneal fluid of women with endometriosis (92), and this growth factor significantly enhances the proliferation of human OSE cells in a dose-dependent manor (93).

In summary, these key inflammatory modulators, hormones, and growth factors are maintained at high levels by immune and endometryotic cells at the ovarian endometriosis foci. The resulting microenvironment is similar to that found in ovarian cancer, and malignant OSE cells are shown to use these modulators for proliferation, evasion of apoptosis, and evasion of immune surveillance. It is reasonable to surmise that sustained elevation of these biologic modulators in the ovarian endometriosis microenvironment may promote malignant transformation in susceptible OSE cells.

CLINICAL IMPLICATIONS

Diagnosis of Endometriosis

Owing to its malignant potential, endometriosis requires particular vigilance during diagnosis and treatment. Routine imaging studies have not been able to diagnose either endometriosis or malignant transformation of endometriotic disease. However, recently, magnetic resonance imaging evidence of malignant transformation within an endometrioma has been suggested. The finding that was most important for

a diagnosis of malignant change was the presence of one or more contrast material–enhanced mural nodules within a cystic mass. Enlargement of the endometrioma and the disappearance of shading within the mass on T2-weighted images may be suggestive of malignant transformation (94).

Diagnosis has thus far been limited to direct observation through surgery; the appearance of endometriosis has been described as having a protean, or widely varied, appearance, making a gold standard for diagnosis difficult. Proteomic techniques are now being used to identify proteins that are potential biomarkers for the disease. This strategy uses mass spectrometry to identify, purify, and sequence proteins directly rather than through mRNA and complementary DNA intermediates. It has been noted that glycodelin-A biosynthesis is reduced in endometriosis compared with unaffected cycle-matched control subjects (95). Identifying an accurate marker will be challenging, owing to the likely multifactorial etiology of endometriosis and the variations between individuals and varying influences of steroid hormones during the menstrual cycle. However, proteomic profiling in combination with bioinformatics software has the potential for major diagnostic contributions for the endometriosis disease process (95). These updated techniques may have a complementary role in diagnosing patients with endometriosis, and thus a population with an increased cancer risk.

Treatment of Endometriosis

The correlation of endometriosis and malignancy may require earlier and more meticulous surgical intervention for complete disease treatment. Currently there are no established recommendations for women with endometriosis who have completed childbearing. Special consideration should be given toward bilateral oophorectomy in women with endometriosis undergoing hysterectomy near the age of menopause, especially those with a history of infertility, a family history of ovarian and breast cancer, or ovarian hyperovulation stimulation. Endometriosis is treated by surgical intervention in conjunction with hormone suppression. Surgical approaches for pelvic pain consist of either conservative or extirpative management. Efficacy of surgical treatment of endometriosis for chronic pelvic pain and infertility is well established (96–99). A literature review in 2007 by Bosteels et al. (100) accepted that enough evidence exists to incorporate the use of diagnostic laparoscopy in the current fertility practice.

Conservative surgical techniques are used for reproductive preservation to restore anatomic relationships by division of adhesions, excision of peritoneal implants, resection of ovarian lesions, restoration of the cul-de-sac, uterosacral nerve ablation, or presacral neurectomy. Because endometriosis appears to be estrogen dependent, any kind of oral hormonal therapy will improve pain and can be used as adjuvant therapy after surgical resection of endometrial implants.

The extirpative approach to surgical management consists of hysterectomy and bilateral salpingoophorectomy in cases of failed conservative therapy or undesired fertility. Retention of any ovarian tissue continues estrogen stimulation of endometrial implants and shows increased rates of symptom recurrence or further surgery.

Postoperative hormone replacement therapy in patients with endometriosis after extirpative surgical management remains controversial, particularly in severe cases and those with residual endometriosis after resection. Unopposed estrogen in posthysterectomy patients may still hold a risk due to possible degeneration of endometrial foci from normal to hyperplastic, atypical, or malignant epithelium. Therefore, postoperative hormone replacement in women with known residual endometriosis may benefit from addition of progestins. Hormone replacement therapy after radical surgery can be initiated with progestins followed by combined estrogen-progesterone. Although use of progestins has not been shown to increase the risk of malignant transformation in endometriosis foci, it must be noted that multiple lines of evidence do suggest that regimens with both estrogen and progesterone versus estrogen alone are associated with greater risk of breast cancer (101). Therefore, patient counseling and treatment individualization is highly recommended. There are also case reports of endometrioid carcinomas arising from ovarian endometriosis in women on tamoxifen therapy (102). Therefore, women with endometriosis on tamoxifen may benefit from increased surveillance. There are preliminary data on the use of macrolide and the immunosuppressant rapamycin to induce regression of endometriotic lesions. Immunosuppressive doses of rapamycin have been suggested to reduce VEGF, thereby reducing angiogenesis (103). This approach has been shown to reduce tumor growth and metastasis, and its role in inhibiting endometrial implants is currently being investigated. This antiangiogenic treatment could reduce growth of endometriosis, thereby eliminating its long-term malignant potential. Aromatase inhibitors have also shown significant benefit in reducing pelvic pain due to endometriosis. One pilot study showed laparoscopic evidence of eradication of pelvic implants and pelvic pain reduction. Phase II clinical trials have concluded that aromatase inhibitors: 1) effectively treat endometriosis induced pelvic pain resistant to first line therapies; 2) are the agent of choice for postmenopausal endometriosis; 3) should be used in combination with a GnRH analogue, progestin, or combination oral contraceptive for ovarian suppression; and 4) have side effect profiles that are favorable and, for most regimens, do not include bone loss (104).

Clinical Patterns

In a clinical and histologic correlation study by Deligdisch et al. (41), ovarian endometriosis was present in 40 out of 76 cases, of which 39 were nonserous carcinomas. Of the 54 patients with nonserous carcinomas, 3 presented with asymptomatic pelvic masses, 33 with painful pelvic masses, all with associated ovarian endometriosis, and 20 with vaginal bleeding. Therefore, over two-thirds of stage I ovarian carcinomas were nonserous, diagnosed early because of their associated symptomatic pathology, mainly endometriosis with pelvic pain. Therefore, ovarian malignancies in patients

with a history of endometriosis and adenexal masses should be kept in mind. At the present time, in the absence of sensitive imaging and tumor markers for preoperative diagnosis, vigilant follow-up of these patients is recommended.

Endometriosis-associated ovarian cancers may be a distinct subtype of epithelial ovarian cancer with unique characteristics. Independent studies show uniform results when comparing EAOC cases and non-EAOC cases regarding stage, pathologic subtype, residual tumor, and survival (105). EAOC cases are diagnosed more frequently at stage I, are predominantly endometrioid and clear cell histologic subtypes rather than serous, and have fewer cases of residual tumor and better survival. For patients with disease confined to the site of origin, survival is 82%–100%, although disseminated intraperitoneal disease has a poor prognosis of 0%–12% 5-year survival. Women with endometriosis-associated cancer most likely represent a unique subgroup of ovarian cancer patients, perhaps requiring different therapy.

CONCLUSIONS

Although not yet fully delineated, there is a strong relationship between endometriosis and ovarian cancer. Advancements in more precise diagnostic, prognostic, and treatment options for endometriosis are needed to address early ovarian cancer. In particular, further elucidation of the involved genetic and immune mechanisms of endometriosis is necessary. Overall, once the transition from benign endometriosis to atypical and malignant tissue is clarified, marker expression can be analyzed to guide clinical management and outcome. Genomics and proteomics may facilitate the development of these diagnostic tools. At this time, however, surgical resection followed by medical treatment remains the primary method of treatment of endometriosis. With the correlation of endometriosis and ovarian cancer continuing to strengthen over time, appropriate and timely resection and elimination of disease should be practiced.

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