MINI-REVIEW

# Endometriosis, Leiomyoma and Adenomyosis: the Risk of Gynecologic Malignancy

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## Abstract

**The aim of this review article was to evaluate the relationship and the possible etiological mechanisms between endometriosis, leiomyoma (LM) and adenomyosis and gynecological cancers, such as ovarian and endometrial cancer and leiomyosarcoma (LMS). MEDLINE was searched for all articles written in the English literature from July 1966 to May 2013. Reports were collected systematically and all the references were also reviewed. Malignant transformation of gynecologic benign diseases such as endometriosis, adenomyosis and LM to ovarian and endometrial cancer remains unclear. Hormonal factors, inflammation, familial predisposition, genetic alterations, growth factors, diet, altered immune system, environmental factors and oxidative stress may be causative factors in carcinogenesis. Early menarche, low parity, late menopause and infertility have also been implicated in the pathogenesis of these cancers. Ovarian cancers and endometriosis have been shown to have common genetic alterations such as loss of heterozygosity (LOH), PTEN, p53, ARID1A mutations. MicroRNAs have also been implicated in malignant transformation. Inflammation releases proinflammatory cytokines, and activates tumor associated macrophages (TAMS) and nuclear factor kappa b (NF-KB) signaling pathways that promote genetic mutations and carcinogenesis. MED12 mutations in LM and smooth muscle tumors of undetermined malignant potential (STUMP) may contribute to malignant transformation to LMS. A hyperestrogenic state may be shared in common with pathogenesis of adenomyosis, LM and endometrial cancer. However, the effect of these benign gynecologic diseases on endometrial cancer should be studied in detail. This review study indicates that endometriosis, LM, adenomyosis may be associated with increased risk of gynecological cancers such as endometrial and ovarian cancers. The patients who have these gynecological benign diseases should be counseled about the future risks of developing cancer. Further studies are needed to investigate the relationship between STUMPs, LMS and LM and characteristics and outcome endometrial carcinoma in adenomyotic patients.**

**Keywords:** Endometriosis - adenomyosis - leiomyoma - gynecologic cancers

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## Introduction

Gynecologic cancers lead to high morbidity and mortality rates around the world. A total of 790,740 new cancer cases and 275,370 deaths from cancer in women are projected to occur in the United States in 2012 (Siegel et al., 2013). Among gynecologic malignancies ovarian cancer is the leading cause of death followed by endometrial and cervical cancers (Siegel et al., 2013).

Many factors have been associated with the increased risk, especially in ovarian and endometrial cancers such as hormonal factors, inflammation, familial predisposition, genetic alterations, growth factors, diet, altered immune system, environmental factors and oxidative stress. Some demographic factors such as early menarche, low parity, late menopause and infertility have also been implicated in the pathogenesis of these cancers.

Endometriosis, adenomyosis and uterine myomas are benign diseases that commonly affect the women of reproductive age. All of these 'womb' diseases are known to be estrogen dependent benign tumors. Inflammatory, environmental, dietary and genetic factors may play a role in the development of these benign tumors. They also have close relationship with each other and sometimes all these benign diseases may be found in the same patient.

Endometriosis, adenomyosis and uterine myomas share the common pathophysiology with some gynecologic malignancies such as ovarian and endometrial cancer, and there is growing evidence that these benign diseases may undergo malign transformation. This review would discuss the evidence that suggests correlations between these diseases and ovarian and endometrial cancers.

## Literature Search

This article reviews English literature for the studies that investigate the relationship between endometriosis, leiomyoma (LM) and adenomyosis and gynecologic

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cancers such as ovarian, endometrial cancers and leiomyosarcomas (LMS). We searched the MEDLINE (Pubmed) database between Jul 1966 and May 2013 using the keywords 'endometriosis', 'LM', 'adenomyosis', 'ovarian cancer' 'LMS' and 'endometrial cancer'. Reports were collected systematically and all the references were also reviewed.

## Endometriosis

*Endometriosis and the risk of gynecologic cancer*

Data from large cohort and case control studies have shown that endometriosis patients have increased risk of ovarian cancer (Ness et al., 2000; 2002; Olson et al., 2002; Borgfeldt and Andolf, 2004; Modugno et al., 2004; Brinton et al., 2005a; Kobayashi et al., 2007; Rossing et al., 2008). These carcinomas have been termed as endometriosis associated ovarian cancer (EAOC). The histologic subtypes of EAOC are clear cell carcinomas (CCC) (40-55%), endometrioid carcinomas (EAC) (20-40%), and less than 10% of them are serous and mucinous subtypes (Worley et al., 2013).

The risk of ovarian cancer arising from endometriosis was shown in Table 1 (Brinton et al., 1997; 2004; 2005b; Ness et al., 2000; Borgfeldt and Andolf, 2004; Modugno et al., 2004; Melin et al., 2006; Kobayashi et al., 2007; Nagle et al., 2008; Wu et al., 2009; Aris, 2010). The relative risk was 2.7 in infertile women (Wei et al., 2011). The risk of EAOC is increased with age, inflammation, genetic predisposition, duration of the disease and the presence of endometrioma diameter of 9cm or more (Vlahos et al., 2010; Wei et al., 2011). Oral contraceptive use, tubal ligation, hysterectomy, and pregnancy may offer some protection against EAOC (Nezhat et al., 2008).

*How does malignant transformation of endometriosis occur?*

'Atypia' has been detected in ovarian endometriomas and may be a precancerous status (Terada, 2012). About 60-80% of EAOC cases arise from atypical lesions (Wei et al., 2011). Some studies have demonstrated that there is a direct transition from endometrial gland to atypia and to carcinoma (Nezhat et al., 2008; Wei et al., 2011).

'Metaplasia' has also been found in EAOC, usually seen in precancerous stage that is distinct from atypical endometriosis (Mangili et al., 2012). The relationship between EAOC and metaplasia is unclear however both squamous and mucinous metaplasia was found in association with cancer arising from endometriosis (Mangili et al., 2012).

**Table 1. Epidemiologic Cohort Studies Assessing Ovarian Cancer Risk in Endometriosis Patients**

| Author | Study type | Cohort size | Overall cancer risk |
|---|---|---|---|
| Brinton et al., 1997 | Cohort | 20.686 | 1.2 |
| Ness et al.,2000 | Case control | 767 | 1.7 |
| Brinton et al., 2004 | Cohort | 12.193 | 2.5 |
| Modugno et al., 2004 | Case control | 2098 | 1.3 |
| Borgfeldt , Andolf, 2004 | Case control | 28.163 | 1.3 |
| Brinton et al., 2005a | Cohort | 99.000 | 2.5 |
| Melin et al., 2006 | Cohort | 63, 630 | 1.0 |
| Kobayashi et al., 2007 | Cohort | 6.398 | 8.9 |
| Nagle et al., 2008 | Case control | 142 endometrioid tumors<br>90 clear cell tumors | 2.2 |
| Wu et al., 2009 | Case control | 609 | 1.6 |
| Aris, 2010 | Cohort | 2521 | 1.6 |

Another theory is the 'bad endometrium'. It has been also proposed that mutations in eutopic endometrium can predispose to endometriosis and may lead to malignancy (Gounaris et al., 2011). When PIK3CA- m TOR and Ras-Raf-MAPK pathway activations and PTEN and ARID1A mutations occur in endometrial tissues this 'bad endometrium' may contribute to development of endometriosis and EAOC by retrograde menstruation in some women (Gounaris et al., 2011).

Genetic alterations, heme and free iron induced oxidative stress, inflammation, and steroid hormones may also play important roles in tumorigenesis of EAOC.

*Genetic alterations*

Genomic instability is a known characteristic of cancer (Pérez de Castro and Malumbres, 2012). Moreover, it is well known that most neoplasms are monoclonal in origin (Teixeira and Heim, 2011). It has been suggested that endometriotic cells are also monoclonal and thus may carry a neoplastic potential (Munksgaard and Blaakaer, 2012). 60-100% of endometriotic tissue was found to be monoclonal (Munksgaard and Blaakaer, 2012).

Loss of heterozygosity (LOH) indicates regions of tumor suppressor gene inactivation that is central to the development of malignant tumors. Jiang et al. (1998) reported that although LOH in solitary endometriosis was rare, there was a 20-30% occurrence of LOH in endometriosis that was in close proximity to EAOC (Jiang et al., 1998). Moreover, the occurrence of LOH was 94% in EAOC itself (Jiang et al., 1998). This result indicates a possible malignant genetic transition spectrum between endometriosis and cancer. LOH has been found to be present in many different chromosomes in various patients with EAOC. The greatest occurrence, however, has been found on chromosome 10q and the lowest occurrence has been found on chromosome 17 (Vigano et al., 2006). Sato et al. (2000) found a 56.5% occurrence of LOH on chromosome 10q23.3 in EAOC (Sato et al., 2000).

Another tumor suppression gene that is frequently associated with mutations into cancerous cells is the PTEN gene. PTEN mutations are generally observed in endometrial cysts and tend to occur very early in the pathogenesis of EAOC. This supports the idea that endometrial cysts are precursors to cancer. PTEN inactivation has been found in up to 40% of CCC cases (Tan et al., 2013) and also has a relationship between other serous cancers but to a much lesser degree (Gadducci et al., 2012).

The K-ras oncogene is over-expressed in many forms of cancer. Expression of this oncogene results in the malignant transformation of endometriosis to ovarian cancer (Wei et al., 2011). These mutations in this gene have not been observed in normal endometriosis. However, they have been observed in endometriosis that is located next to ovarian cancer (Otsuka et al., 2004). While PTEN and K-ras have been implicated in EAOC, experimenters have

also found a strong correlation between the combination of these two genes and EAOC.

Mutation and loss of function at the p53 gene is thought to be the most frequent event in ovarian cancer (Gadducci et al., 2012). The p53 gene can be activated to induce several cell responses like differentiation, senescence, DNA repair and inhibition of angiogenesis (Bernard et al., 2013). While these mutations are not particularly common in CCC specifically, they are usually found to some extent in most other forms of cancer (Gadducci et al., 2012). Although p53 mutation is not observed in endometriosis, this mutation is seen in 40-50% of the endometriotic cells those are located in close proximity to ovarian cancer cells (Mandai et al., 2009). This finding points to a definite correlation between p53 mutations and EAOC and warrants further study.

Hepatocyte nuclear factor (HNF)1-β is a transcription factor that is upregulated in most clear cell carcinomas (Kao et al., 2012). Specific expression of HNF1-β was found in endometriosis and clear cell carcinomas, suggesting an early differentiation into clear cell lineage from endometriosis (Kobayashi et al., 2011). HNF1-β dependent pathway inhibits apoptosis and stimulates glycogen synthesis and plays an important role in chemoresistance (Kobayashi et al., 2011).

Wilms tumor suppressor gene (WT1) is a nuclear transcription factor that regulates the expression of insulin growth factor (IGF)-1 and transforming growth factor (TGF)–β which are important in tumorigenesis and angiogenesis (Gupta et al., 2009). A diagnostic panel of WT1, estrogen receptor (ER) and HNF1-β is useful in discriminating clear cell carcinomas from high grade serous ovarian carcinomas (Stewart et al., 2008). WT1 levels in endometriotic stromal cells are significantly down regulated in endometriosis (Attar et al., 2009). It has been reported that down regulation of WT1 in endometrial stromal cells may contribute with increased P450 aromatase expression and estrogen formation in endometriosis (Attar et al., 2009). Microsatellites are repetitive DNA sequences that are found in the human genome. It was first described in colorectal tumors from patients with hereditary nonpolyposis colorectal cancer (Kobayashi et al., 2009). It is associated with defective DNA mismatch repair system to repair errors that occur during DNA replication and has been implicated in accelerated accumulation of single nucleotide mutations and alterations in the length of microsatellite sequences (Srivastava and Grizzle, 2010). Response to DNA damage is crucial in the maintenance of genomic stability and cellular integrity and functional inactivation of these genes has been already related with cancer predisposition (Ali-Fehmi et al., 2006).

Hypermethylation of hMLH1 that is a component of DNA mismatch repair pathway is found to be in 8.6% of endometriotic lesions (Mandai et al., 2009). The high level of microsatellite instability (MSI) or MSI leading to PTEN dysfunction has been evaluated for EOC with the frequencies ranging from 6-37% (Ali-Fehmi et al., 2006; Pal et al., 2008). MSI occurs in 7.9-19.2% of epithelial ovarian carcinomas (Murphy and Wentzensen, 2011). Ali-Fehmi et al. reported that MSI was present in 82.6% cases of endometriosis, in 75% cases of atypical endometriosis and in 53% cases of ovarian carcinoma at chromosome 10q23.3 region (Ali-Fehmi et al., 2006). The frequency of PTEN mutations were elevated in high frequency MSI (Fuseya et al., 2012). All these results indicate that MSI may be involved in malignant transformation of ovarian endometrioma.

MUC1 is a member of the mucin family of molecules and expressed as a type 1transmembrane heterodimer (Finn et al., 2011). It is overexpressed on the majority of adenocarcinomas of the ovary, uterus, breast, pancreas, lung, colon, stomach and prostate, promoting oncogenesis, proinflammatory tumor microenvironment and immunosurveillance (Finn et al., 2011). It is also associated with inflammation (Finn et al., 2011). High levels of MUC1 and MUC1 antibody levels are prognostic for poor clinical response and reduced overall survival in ovarian cancer (Budiu et al., 2011).The presence MUC1 in ovarian endometriosis was shown by immunohistochemistry (Finn et al., 2011).

AT-rich interactive domain 1A [SWI-like] gene (ARID1A) mutations have been demonstrated in EAOC such as CCC and EOC (Maeda and Shih, 2013). The mutations were also found in adjacent endometriotic lesions, but not in distant endometriosis in the same patient (Maeda and Shih, 2013). It is suggested that ARID1A mutation is important in the malignant transformation of endometriosis (Maeda and Shih, 2013). There is also evidence that its inactivation occurs early in the development of carcinogenesis. How ARID1A might contribute the development of EAOC remains to be unclear. EAOC is associated with hypoxia and stress pathways and the loss of ARID1A may lead to a decreased normal response to stress (Birrer, 2010).

Micro RNAs (miRNAs) are small noncoding RNAs that bind to target mRNAs, mediating translational repression and/or mRNA degradation. They are newly identified and found to be associated with human carcinomas. It has been reported that miRNAs may play an important role in endometriotic lesion development (Wang et al., 2013). Endometriosis associated miRNAs may have regulatory functions in hypoxia, inflammation, tissue repair, TGF-β regulated pathways, cell growth, cell proliferation, apoptosis, extracellular matrix remodeling and angiogenesis (Lin et al., 2012). It has been proposed that miRNAs may be associated with malignant transformation (Lam et al., 2012).

*Heme and free iron induced oxidative stress*

Heme and iron are prooxidant and can induce oxidative stress and DNA damage and may increase the risk of cancer (Tanase et al., 2012). Retrograde menstruation and hemorrhage in the endometrioma may play a role in carcinogenesis (Tanase et al., 2012). Oxidative stress activate growth related signaling pathways including mitogen activated protein kinase ERK ½ (Son et al., 2013). In cancer modulation reactive oxygen species (ROS) production control tumor cell proliferation, apoptosis and mutations in mitochondrial DNA resulting in respiratory complex I deficiency that increases ROS production and enhance metastatic potential of tumor cells (Cheng et al.,

2013). Heme and iron act as proinflammatory molecules. These molecules activate nuclear factor kappa b (NF-KB), activator protein-1 (AP-1), specificity protein-1 (SP-1) (Zhang and Frei, 2003). Heme also activates neutrophil responses; neutrophil chemotaxis, cytoskeleton reorganization, oxidative burst, production of IL-8 and transcriptional activation (Graça-Souza et al., 2002). They can induce genetic mutations via production of ROS that all of them may be implicated in the development of cancer (Munksgaard and Blaakaer, 2012).

*Inflammation*

Chronic inflammation with genetic alterations promotes the progression of malignant EAOC. Endometrial cells chronically stimulate the immune system and increased levels of cytokines and growth factors have been observed in peritoneal fluid of women with endometriosis (Du et al., 2013). Inflammatory cells may promote angiogenesis, cell proliferation, inhibition of apoptosis, invasion, metastasis, and production of ROS that contribute to DNA damage and mutations.

Tumor necrosis-α (TNF-α) levels were found to be similar in patients with endometriosis and ovarian cancer (Munksgaard and Blaakaer, 2012). It has been reported that growth hormone and IL-6 were increased both in endometriomas and endometrioid adenocarcinomas (Slater et al., 2006). Ectopic endometrium was at least 100 times more sensitive to IL-1beta compared with eutopic endometrium (Wu et al., 2005). IL-1beta upregulates cyclooxygenase-2 (COX-2) expressions that leads to increased synthesis of prostaglandin E2 (PGE2). PGE2 regulates key processes for tumor growth, angiogenesis, proliferation, and inhibition of apoptosis (Zhang and Daaka, 2011). Moreover, COX-2 was found to be increased in epithelial ovarian cancer, correlating with the stage of the disease (Lee et al., 2013).

Toll like receptors (TLRs) and their intracellular signaling components are important cellular pathways that are associated with inflammatory process, cancer progression and chemoresistance (Yu et al., 2012). They have a crucial role in endometriosis and ovarian cancer (Kajihara et al., 2011; Kim et al., 2012). ROS induce inflammatory signaling through TLRs (Kajihara et al., 2011). They serve as cell surface sensors that can initiate pathways leading to proliferation, and also as mediators that regulate the infiltrating immune cells for further support for cancer progression (Kim et al., 2012).

Most ovarian tumors are infiltrated by large number of macrophages. These tumor associated macrophages (TAMS) are key component of the tumor stroma and are essential for angiogenesis and matrix remodeling. TAM promotes tumorigenesis via Wnt/β-Catenin signaling (Newman and Hughes, 2012). It inhibits adaptive immunity by the release of chemokines such as CCL-8 that release immunosuppressive mediators including IL-10 and TGF-β (Wei et al., 2011). TAM signaling also promotes angiogenesis by production of epidermal growth factor, TGF-β and chemokines and stimulates proliferation of NF-KB, migration inhibitory factor (MIF), and IL-1 (Wei et al., 2011). TAM is also associated with extracellular tissue remodeling activity through expression and release of matrix metallopeptidases (MMP) 2 and 9 and urokinase plasminogen activator (UPA) (Yeh et al., 2013).

NF-KB proteins are transcription-factor regulating genes that have been associated with inflammation (IL-1, IL-6, IL-8, inducible nitric oxide synthase [iNOS], COX-2), immunity (interferon-γ [IFN-γ], TNF-α, regulated upon activation, normal T-cell expressed and secreted [RANTES], intercellular adhesion molecule-1 [ICAM-1]), apoptosis(cellular inhibitor of apoptosis proteins [c-IAP], A1/Bfl1, cellular FLICE-like inhibitory protein [c-FLIP], p53, Bax), cell proliferation (cyclin D1, c-myc, epidermal growth factor [EGF]), tissue invasion (MMP-1), urokinase-type plasminogen activator [uPA]), and angiogenesis (vascular endothelial growth factor [VEGF]) (González-Ramos et al., 2010). These cell processes are involved in the development of endometriosis and ovarian cancer (González-Ramos et al., 2010). NF-KB is active in tumor cells and can also mediate metastasis through the expression of various adhesion molecules including ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and endothelial-leukocyte adhesion molecule -1(ELAM-1) (van de Stolpe et al., 1994). Inhibition of NF-KB in cancer cells increases apoptosis (Zerbini et al., 2011). It has been also proposed that NF-KB inhibitors may be added to chemotherapy to enhance the therapeutic outcomes (Zerbini et al., 2011).

MIF is another important key regulator of immune and inflammatory response in tumor progression such as TNF-α and IL-1 (Yaddanapudi et al., 2013). MIF was found to be increased in peritoneal fluid of women with endometriosis and its activity was also higher in active ectopic endometrial implants (Herrmann et al., 2007). Ovarian borderline tumor, ovarian carcinomas, and malignant ascites of patients with ovarian cancer express significant MIF protein.

MIF affects protumorigenic pathways in many different ways. TAMS activation was one of these pathways that contribute to tumor progression and the development of metastasis (Obeid et al., 2013). Loss of MIF is associated with DNA damage and Skp1-Cullin-F-box dependent degradation of specific cell cycle regulators, leading to tumorigenesis. MIF stimulates COX-2 synthesis and PGE2 secretion in ectopic endometrial cells (Carli et al., 2009).

In summary inflammation is a hallmark of endometriosis with local and systemic effects. Inflammation promotes release of proinflammatory cytokines, and induces DNA damage, and transcriptional changes that are especially important in proliferation, DNA repair and genetic mutations.

*Sex steroid hormones*

It has been widely known that estrogen has been linked in the pathophysiology of gynecologic malignancies such as endometrium and ovarian cancer. Endometriosis is also estrogen dependent disease and hyperestrogenism may be associated with the malignant transformation of endometriotic cysts (Worley et al., 2013).

Steroidogenic acute regulatory protein (STAR) regulates the initial entry of cytosolic cholesterol into the mitochondria and facilitates the initial step of estrogen

formation. It is also widely known that the enzyme aromatase catalyzes the conversion of androstenedione and testosterone to estrone and estradiol. Thus, STAR and aromatase are the key steps in estrogen production. They are normally absent in eutopic endometrium, but found at high levels in patients with endometriosis (Sacco et al., 2012).

Steroidogenic factor-1 (SF-1), C/EBPs and CREB are transcriptional enhancers that are responsible for PGE2-cAMP dependent STAR and aromatase promoters in endometriosis (Bulun et al., 2005). These promoters remain quiescent under the influence of inhibitory transcription factors such as chicken ovalbumin upstream promoter-transcription factor (COUP-TF) and corepressor WT-1 in normal endometrial cells (Attar et al., 2009). SF-1 binding activity was higher in endometriotic cells whereas the inhibitory COUP-TF and WT-1 was absent or minimal in endometriotic cells when compared with normal endometrium (Attar et al., 2009).

The nuclear receptor NR5A1, which is present in endometriosis and absent in endometrium serves as another the key transcription factor that is responsible for mediating PGE2-cAMP- dependent induction of STAR, aromatase and possibly other steroidogenic genes in endometriotic stromal cells (Wei et al., 2011). The absence of NR5A1 in endometrial cells plays a major role in the lack of responsiveness of steroidogenic genes to PGE2 or cAMP analogs (Wei et al., 2011). All these data suggest that the transcriptional environment within endometriotic cells is permissive for estradiol synthesis that is further enhanced by the PGE2.

The enzyme 17β-hydroxysteroid dehydrogenase type II, which catalyzes the inactivation of estradiol to less potent estrone was absent in endometriosis. In sum, the potent estradiol is increased while inactivation is decreased resulting in higher estrogenic activity.

It has been reported that the carcinogenic action of estrogen is mediated through the ERα whereas ERβ did not seem to be involved (O'Donnell et al., 2005). Increased expression of ERα has also been shown in active endometriosis (Pellegrini et al., 2012). ERα mediates estrogen related proliferation through the cyclin D1 gene transcription (Pellegrini et al., 2012) and ERβ oppose ERα, plays an inhibitory role in the expression of IGF-1 and VEGF in the endometrial stroma (Bukulmez et al., 2008). Treatment of ERβ agonist resulted in complete regression of the endometriotic lesions in the animals (Harris et al., 2005). It has been also suggested that ERβ agonists may also have anti-inflammatory effects on immune cells (Bukulmez et al., 2008).

Progesterones generally repress ER, inhibiting the effects of estrogens at the cellular level. There is some evidence that endometriosis has a relative progesterone resistance. The inhibitory progesterone receptor A (PRA) is present and the stimulatory PRB is absent in endometriotic lesions (Bukulmez et al., 2008). PRC which antagonizes PRB is also overexpressed in endometriosis that is associated elevated inflammatory cytokines and NF-KB activation (Bukulmez et al., 2008). PRC may be responsible for disease progression (Condon et al., 2006). Progesterone also activates retinoic acid pathway (Kim et al., 2013). Retinoic acid induces enzyme HSD17B2 that catalyzes conversion of potent estradiol to estrone. Lower stromal PR leads to deficient formation of retinoic acid that contributes to accumulation of estradiol (Kim et al., 2013).

## Leiomyomas

*Leiomyomas and the risk of gynecologic cancer*

Uterine LM is a common neoplasm. It occurs in nearly 40% of women of reproductive age. Leiomyosarcomas (LMS) are the most common sarcomas that are reported to be in only 0.1-0.3% of LMs.

*Pathogenesis*

The pathogenesis of LMS is poorly understood. It is unknown whether these tumors arise de novo or from preexisting LMs. It has been reported that the progression of LM to LMS is rare, so some investigators believe that the most LMS are sporadic and arise de novo (McDonald et al., 2011). This hypothesis was supported by the finding that the miRNA expression profiles between LMS and LM were shown to be different (Kowalewska et al., 2013). In contrast, several cases of histologically proven LMS arising in preexisting LM of the uterus have been reported (Kim et al., 2010; Yanai et al., 2010; McDonald et al., 2011). It has been considered that benign compartment is a precursor lesion to LMS that was showed both immunohistochemically and cytogenetically (Yanai et al., 2010; McDonald et al., 2011). Rearrangements at chromosome 10q22 in cellular LM were also seen in LMS (Mittal and Joutovsky, 2007). The loss of short arm of chromosome 1 in cellular LM may contribute to malignant transformation to LMS (Hodge and Morton, 2007). Nearly all the genetic aberrations found in LM like areas were also seen in LMS in another study (Mittal et al., 2009). In addition LMS areas had additional genetic aberrations (Mittal et al., 2009). Some genes that are down regulated in LMS such as GAS1, DUSP1, BTG3, and NBL1 may be upregulated in LM (Quade et al., 2004). LM like areas showed amplification in many oncogene and transcription factor genes including MED12, C-JUN, Cks-1, Fyn, K-Ras and ELK-3 (Mittal et al., 2009; Mäkinen et al., 2011). MED12 mutations in LM can lead to oncogenesis through the Wnt/β-catenin pathway (Mäkinen et al., 2011). It has been also suggested that LMS could arise from the preexisting LM that has a symplastic or cellular morphology (Mittal et al., 2009). Smooth Muscle Tumors of Undetermined Malignant Potential (STUMP) are the other uterine tumors that are poorly understood. They encompass a large group of neoplasms representing the entire spectrum from benign to malignant (Pérot et al., 2012). Histologic distinction between malignant and benign smooth muscle tumors remains challenging. It has been reported that they can have metastatic activities or undergo malignant transformation to LMS. According to the current WHO classification if the tumor shows any unusual histologic combinations that do not meet the Stanford criteria for LMS, a diagnosis of STUMP is appropriate (Ip and Cheung, 2011).

It has been reported that immunohistochemical stains, including p16, p53, MIB-1, p21, Twist, bcl-2,

ER and PR, may serve to identify STUMP with a higher risk of recurrence (O'Neill et al., 2007; Atkins et al., 2008; D'Angelo et al., 2009; Ip et al., 2009; Lee et al., 2009; Unver et al., 2011). STUMP expresses genes that are involved in cell proliferation and regulation of the cell cycle including CDKIN2A (Ip and Cheung, 2011). Recurrence rates are slower and delayed when compared with LMS (Ip and Cheung, 2011). STUMPs that are followed by recurrences are considered to be low grade tumors. MED12 mutations have been implicated in transcription regulation and act as a bridge between DNA binding transcription factors and RNA polymerase II initiation (Taatjes, 2010; Conaway and Conaway, 2011). MED12 mutations have been identified in LM, STUMP and LMS (Pérot et al., 2012; McGuire et al., 2012). It has been suggested that subsequent acquired alterations lead to malignant evolution and mutations in LM may contribute to the development of STUMP and LMS (Pérot et al., 2012; McGuire et al., 2012).

mTOR pathway plays a significant role in cell signaling pathways which promote tumorigenesis that directly regulate protein synthesis, cell-cycle progression, cell growth and proliferation (Pandurangan, 2013). Dysregulation of PI3-K/Akt/mTOR pathway has been implicated in the pathogenesis and progression of many human cancers (Pandurangan, 2013). It has been demonstrated that nuclear p-mTOR, nuclear p-Akt and phospholipase D1 are overexpressed in LMS>STUMP>LM respectively (Dhingra et al., 2010). Cell progression in STUMP towards LMS is observed (Dhingra et al., 2010). Acrogranin, another pluripotent growth factor that mediates cell cycle progression and cell motility, is increased in cancers and also has important roles in wound repair that is overexpressed in LMS (Matsumura et al., 2006). It has been found that forced overexpression of acrogranin in immortalized uterine smooth muscle cells contribute to malignant transformation (Matsumura et al., 2006).

It has been also reported that LM may be associated with increased risk of endometrial cancer (Rowlands et al., 2011). Women diagnosed with LM after the age 30 and the long duration of the disease may lead to this increased risk (Rowlands et al., 2011). The risk was also higher in pre and perimenopausal nonobese women (Rowlands et al., 2011). It has been suggested that premenopausal women with LM should be monitored more closely (Rowlands et al., 2011). However, another study found that obesity and postmenopausal status with the history of LM is associated with endometrial cancer (Fortuny et al., 2009). The majority of these findings support the hormonal etiology of both disorders. Further studies are needed to investigate the relationship between LM and endometrial cancer.

## Adenomyosis

*Adenomyosis and the risk of gynecologic cancer*

Adenomyosis is a common benign pathology that is defined by the presence of endometrial glands and stroma within the myometrium. It has been reported that adenomyosis is associated with endometrial cancer (Boes et al., 2011; Musa et al., 2012). The incidence of these two conditions in hysterectomy patients changed from 10% to 70% (Musa et al., 2012).

*Pathogenesis*

The mechanism of the development of endometrial cancer in patients with adenomyosis remains unclear. Previous reports have suggested that adenomyosis can undergo malignant transformation and may be a precursor lesion to adenocarcinoma (Mittal and Barwick, 1993; Kucera et al., 2011). However, no study has demonstrated the natural transformation of adenomyosis to adenocarcinoma. There is a frequent association between adenomyosis and other estrogen dependent benign diseases such as endometrial polyps, anovulation, hyperplasia, LM suggesting that hyperestrogenic state may share the common pathogenesis of these gynecological diseases and endometrial cancer. It has been found that annexin A2 is a key mediator in endometrial tissue growth, metastasis, and angiogenesis (Zhou et al., 2012). p53 positivity was found in hyperplastic and atypical epithelia of carcinoma in adenomyotic patients (Abushahin et al., 2011).

It has been reported that endometrial cancers involving adenomyosis was associated with a low histologic grade, a history of hormonal use and more favorable prognosis (Ismiil et al., 2007a). However, other data suggest that adenomyosis is related with deep myometrial invasion (Ismiil et al., 2007b). Musa et al. (2012) found that there was a close relationship between adenomyosis and lower tumor grade, less myometrial invasion, negative lymphovascular space invasion and negative lymph nodes (Musa et al., 2012). This result shows that endometrioid tumor with adenomyosis are hormonally responsive, well differentiated, and more likely to be diagnosed earlier while it would be still confined to uterus. Further studies are needed to help us to understand the effect of adenomyosis on endometrial cancer.

## Conclusions

In conclusion, this review shows that endometriosis, LM and adenomyosis are at significantly increased risk for the development of gynecological cancers such as ovarian cancer and endometrial cancer. The risk of EAOC is increased with age, hyperestrogenism, inflammation, genetic predisposition, early diagnosed and long standing endometriosis, the presence of large endometrioma and infertility. STUMPs are considered to be low grade tumors and although it is not clear, some studies suggest that STUMP and LMS may arise from mutant precursor cells of LM. There is also a close relationship between LM, adenomyosis and endometrial cancer. It has been suggested that adenomyosis may be associated with less myometrial invasion, negative lymphovascular space invasion, lower tumor grade and negative lymph nodes. Endometriosis, LM, adenomyosis and gynecological cancers such as endometrial and ovarian cancers share the common pathogenic mechanisms that include hormonal factors, inflammation, familial predisposition, genetic alterations, growth factors, diet, altered immune

system, environmental factors and oxidative stress. Other factors such as age, infertility, duration of the disease are also important cofactors. The patients who have these gynecological benign diseases should be counseled about the future risks of developing endometrial and ovarian cancer. Future studies are needed to investigate the relationship between STUMPs, LMS and LM and the outcome of endometrial cancers in adenomyotic patients.

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