Review Article

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How Benign is Endometriosis: Multi-Scale Interrogation of Documented Evidence

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Abstract

Endometriosis is an inflammatory disease characterized by the presence of endometrium-like tissue outside the uterus primarily on pelvic organs and tissues. It affects up to 15% of women in the reproductive age group and is often associated with pelvic pain and subfertility. Different theories explain how retrograde menstruation gives rise to endometrial deposits at ectopic sites, and how several other factors are involved in the progression of the disease. Its final diagnosis is established through direct visualization at laparoscopy or surgery followed by histological confirmation. Available epidemiological reports along with histopathological observations and molecular studies shed interesting light on the pathogenetic basis of different variants of the disease like deep infiltrating endometriosis and ovarian endometriosis. Evidence also suggests that endometriosis is a neoplastic condition which serves as a precursor of ovarian and endometrial cancers. In the present review, we have attempted to take a stock of the current epidemiological and molecular knowledge regarding endometriosis-associated cancers and develop a model of functional network with interactions among critical genomic factors regulating cellular processes leading to fibrotic reaction. It is being conjectured that cyclic bleeding associated with inflammatory and oxidative stress followed by repeated tissue injury and repair along with recurrent estrogenic stimulation and ovulatory events in the pelvic environment bring about the complex phenotype of atypical endometriosis and associated neoplasm with a trade-off malignant transformation in high risk population. Finally, we have presented an algorithm for pre-emptive monitoring and management of endometriosis-associated cancers.

Keywords: Endometrial cancer, Endometriosis, Endometriosis-associated cancer, miRNA, Oncogenes, Ovarian cancer, Tumor suppressor genes

Abbreviations: 4EBP1: Eukaryotic translation initiation factor 4E Binding Protein 1; AE: Atypical Endometriosis; aHR: Adjusted hazard Ratio; AKT1: AKT serine/threonine Kinase 1; ARID1A: AT-rich Interaction Domain 1A; BAF250a: Barrier to Autointegration Factor; BCOR: BCL6 Corepressor; CBFB: Core-Binding Factor subunit Beta; CCL: Chemokine Ligands; CCND1: Cyclin D1; CCR1: C-C motif Chemokine Receptor 1; CDH1: Cadherin 1; CDKN2A: Cyclin Dependent Kinase inhibitor 2A; CE: Control (disease-free) Endometrium; CHEK1: Checkpoint Kinase 1; CI: Confidence Interval; CLOCK: Clock circadian regulator (Circadian Locomotor Output Cycles protein Kaput); CTNNB1: Catenin Beta 1; DIE: Deep Infiltrating Endometriosis; DNMT1: DNA Methyltransferase 1; EAC: Endometriosis-Associated Cancer; EAO: Endometriosis-Associated Ovarian Cancer; EC: Endometrial Cancer; EE: Eutopic Endometrium from proven endometriosis; EEC: Endometrial Endometrioid Cancer; EMT: Epithelial-Mesenchymal Transition; EOC: Epithelial

Ovarian Cancer; ERBB: Erb-B2 Receptor tyrosine kinase 2; ESR1: Estrogen Receptor 1; ET: Ectopic Tissue; FBXW7: F-Box and WD repeat domain containing 7; FGFR2: Fibroblast Growth Factor Receptor 2; FMT: Fibroblast-to-Myofibroblast Trans-differentiation; FOXA1: Forkhead box A1; FOXO1: Forkhead box O1; GATA3: GATA binding protein 3; GOF: Gain of Function; HMG1: High Mobility Group box 1; HRAS: Harvey Rat Sarcoma viral oncogene homolog; IGFBP1: Insulin like Growth Factor Binding Protein 1; KRAS: KRAS proto-oncogene; GTPase; Let-7: Lethal (let-7) family; LOF: Loss of Function; LOH: Loss of Heterozygosity; MAP2K4: Mitogen-Activated Protein Kinase kinase 4; MAP3K1: Mitogen-Activated Protein Kinase Kinase 1; MAX: MYC Associated factor X; MMP: Matrix Metalloproteinase; MnSOD: Manganese Superoxide Dismutase; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; MSY: Male-Specific region of the human Y chromosome; mTOR: Mammalian Target of Rapamycin; MYC: MYC proto-oncogene; bHLH transcription factor; NF2: Neurofibromin 2; NOTCH1: Notch receptor 1; OC: Ovarian Cancer; OE: Ovarian Endometriosis; OR: Odds Ratio; PE: Peritoneal Endometriosis; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic subunit Alpha; PIK3R1: Phosphoinositide-3-Kinase Regulatory subunit 1; POTSFs: Proto-oncogenes with Tumor Suppressor Functions; PPP2R1A: Protein Phosphatase 2 scaffold subunit Aalpha; PTEN: Phosphatase and Tensin homolog; QTL: Quantitative Trait Locus; ROS: Reactive Oxygen Species; RR: Relative Risk; RUNX1: Runt related transcription factor 1; RVE: Rectovaginal Endometriosis; SCF: Stem Cell Factor; SIR: Standardized Incidence Ratio; SIRT1: Sirtuin 1; SMM: Smooth Muscle Metaplasia; SPOP: Speckle Type BTB/POZ Protein; SRR: Summary Relative Risk; STAT3: Signal Transducer And Activator of Transcription 3; SWI/SNF: Switch/Sucrose Non-Fermentable; TBL1XR1: Transducin Beta Like 1 X-Linked Receptor 1; TBX3: T-box 3; TGF-beta 1: Transforming Growth Factor-beta; TIMP3: Tissue Inhibitor of Metalloproteinases 3; TP53: Tumor Protein p53; TWIST1: Twist basic helix-loop-helix Transcription factor 1; VEGF: Vascular Endothelial Growth Factor; ZEB1/ZEB2: Zinc finger E-box-binding homeobox 1/2.

Introduction

Endometriosis is characterized by the presence of endometrial cells at ectopic sites, primarily on the pelvic peritoneum and pelvic organs. Adenomyosis, on the other hand, is characterized by the abnormal presence of endometrial tissue within the uterine myometrium. Figure 1 shows a few typical histological features of endometriosis. It is rather a common disease affecting up to 15% women in the reproductive age with symptoms of pelvic pain and subfertility. It is considered as an estrogen-mediated chronic inflammatory condition [1]. Several reproductive factors are known to be associated with the increased risk for endometriosis, such as early age at menarche, short menstrual cycle length, parity and oral contraceptive use [2]. Patients suffering from endometriosis often undergo surgical intervention, but it generally recurs [3]. There are three types of endometriosis: superficial peritoneal endometriosis (PE), ovarian endometriosis (OE) and rectovaginal endometriosis (RVE), also known as deep infiltrating endometriosis (DIE). Each type bears distinctive pathophysiological features. For example, rectovaginal endometriotic nodules generally show glandular epithelium deeply embedded in the fibromuscular tissue with scanty stroma [4,5], while OE may present with little endometrial epithelium [6].

Figure 1: Examining endometriosis. Laparoscopic view of right ovarian endometrioma with severe adhesion obliterating the pouch of Douglas (A). Histopathological features of endometriosis showing ovarian endometriotic cyst with circumscribed stromal nodule and epithelial lining seen at low magnification (B), mildly stratified epithelium associated with neutrophil infiltrate (C) and detached eosinophilic epithelial strips associated with extravasated erythrocytes (D) seen at higher magnification.

Several cellular pathophysiological processes like enhanced cell survivability and proliferation, anomalous immune-inflammatory responses, epithelial-mesenchymal transition (EMT), higher invasive and adhesive capacity, reduction in apoptosis, and enhanced

angiogenesis appear to be integral to the histogenesis of endometriosis [7]. However, the etiopathologic factors that underlie the origins and progressions of this complex disease remain as yet elusive and contentious giving rise to several theories regarding etiopathology of endometriosis. A widely accepted hypothesis is that of 'retrograde menstruation' of Sampson [8] according to which endometrial cells present in refluxed menstrual effluent within the peritoneal cavity attach to various peritoneal surfaces and ovary resulting in histogenesis of endometriosis. According to Hughesdon [9], gradual invagination of endometrial implants on the surface of the ovary into the cortex results in endometriomas [10]. The dissemination of endometrial progenitor cells and bone marrow derived stem cells reaching to eutopic tissue (EE) and ectopic (ET) foci via the lymphatics and/or blood circulation may be another contributing factor towards establishing endometriosis [11]. The 'metaplasia' hypothesis which was first proposed by Meyer [12] posits transdifferentiation of specialized peritoneal lining cells into endometrial cells in metaplastic foci.

Table 1 enlists important predisposing factors, initiators, and propagating factors involved in endometriosis.

Interestingly, Mai et al. [42] based on histopathological studies proposed a model of crucial involvement of stromal cells in the histogenesis of endometriosis as shown in figure 2. According to this hypothesis, histopathologically there are three types of nodules seen in the course of histogenesis of endometriosis: type 1 nodules are formed from the endometrial stromal cells, followed by transformation of the mesothelium into endometrial glands as seen in type 2 nodules and type 3 nodules due to the inductive actions of the endometrial stroma, while other factors of genetic, hormonal and immunological origin affect the proliferative and replicative capacities. The above paradigm is somewhat corroborated by the report of Noe et al. [43], according to which ET lesions may co-develop from independent progenitors for epithelial and stromal cells, since epithelium found clonally and developmentally distinct from stroma and originating from a single circulating endometrial epithelial progenitor cell in the ET niche; it was presumed that these endometrial epithelial progenitor cells do carry "driver" and "passenger" mutations and undergo clonal expansion to form glandular tissue at the ET site [43]. The authors further suggested that blood-borne mesenchymal stem cells might migrate and home at the prospective ET site due to chemotactic activity associated with inflammation and tissue repair and then proliferate giving rise to the

stromal component. A large number of endometriomas in fact show minimal endometrial epithelium and are often covered by fibrotic tissue [6]. Given the fact that fibrosis and myofibroblasts are consistently present in endometriotic lesions and play significant role in the pathogenesis of endometriosis, it has been suggested that fibrosis represents a self-amplifying event towards endometriosis with myofibroblasts playing crucial role in the process and that targeting the fibrotic process may give rise to new approaches for therapeutic interventions to the disease [44].

Figure 2: Three stages of endometriosis development involving stromal cells. Type 1 nodule is characterized by well circumscribed foci predominantly containing stromal cells, very little glandular structure and mild fibrosis (A), while type 2 nodule additionally shows small cystic structure with stromal cells oriented towards the cyst (square brackets) and clear fibromuscular tissue (B), and type 3 nodule typically showing larger cysts with indication of epithelial transformation either with (arrow) and without (arrow head) underlying stroma along with evidence of high fibrotic reaction and fibromuscular tissue (C). Based on such histopathological evidence, a tentative pathogenetic pathway of endometriosis was suggested by Mai et al. [42] as shown in D. According to the proposed model, type 1, 2 and 3 nodules represent a histological continuum in the development of endometriosis. Wavy arrow indicates mediation of inductive process.

Endometriosis in common parlance is taken as a benign tumor-like condition. Based on histopathological and molecular characteristics, predisposing factors and antecedent processes, Varma and colleagues [45] have identified marked similarities between malignancy and endometriosis. The cellular processes which are considered to be crucial during the multistep development of human tumors, for example, unmitigated proliferative

signaling, repression of growth suppressors, higher cell viability, inducement of angiogenesis, and activated invasion and migration are seen in endometriosis [7]. However, fundamental characteristics of cancer, such as genomic instability and the alteration of DNA repair genes are not found in endometriosis [46]. Long back, Scott [47] however raised some serious doubts whether endometriosis is indeed a benign disorder. Based on several lines of evidence, it appears plausible that, endometrial cells refluxed into the pelvic peritoneal niche undergo adhesion, survival and growth resulting in ET lesion due to innate physiological defects, and in the process of disease progression, oncogenic transformation occurs in the vulnerable cells in the high risk population [7,28,30,48-50]. In the present narrative review paper, we make an integrated attempt to undertake evidence-based examination of the link between endometriosis and cancer at different levels.

Endometriosis-associated cancers

In 1925, J.A. Sampson published a paper with a title, "Endometrial carcinoma of ovary, arising in endometrial tissue in that organ" [51]. In order to consider malignant transformation of endometriosis, Sampson [51] proposed following three criteria: (i) the coexistence of benign and malignant tissue in the same ovary which have the same histologic relationship to each other, meaning thereby that tumor exists adjacent to the unequivocal foci of endometriosis, (ii) the carcinoma must actually be seen to arise in this tissue, meaning thereby that there must be an absence of any other primary tumor, and (iii) the presence of clear microscopic evidence of neoplasms originating from endometriosis. In this paper, he put forward his conjecture that endometriosis has the potentiality towards malignant change as much as normal endometrium and that the ET lesion might have a higher propensity. R.B. Scott evaluated several cases of endometriosis reported in the literature including cases from Sampson's report and cases from his own study using Sampson's criteria and he could identify 12 cases of ovarian carcinoma (OC) [47]. Scott, however, commented that an additional criterion must be added: a microscopic section must show the "benign endometriosis running into and continuous with the malignant tissue", meaning thereby that there must exist histological evidence of a transition from endometriosis-associated neoplastic epithelial component or stromal component into malignancy.

Endometriosis is frequently being recognized as a precursor lesion of endometriosis-associated carcinoma

(EAC) in clinical set up [52-55]. It is generally believed that endometriosis - due to transdifferentiation of specialized peritoneal mucosal cells into endometrial cells in the metaplastic foci within a setting of chronic inflammation - may make the lesions predisposed to neoplastic transformation [54,55]. Atypical endometriosis (AE) is often found in direct continuity with the tumor suggesting AE as a transitional form to a malignant phenotype, as discussed below. Generally, AE may be classified based on histopathological criteria like large nuclei with marked pleomorphism, decreased volume ratio of cytoplasm-to-nucleus, cellular stratification with or without epithelial hyperplasia (Figure 3). The incidence of AE in OC reportedly ranged from 4-23% [56-61]. Recently, Stamp et al. [62] in a study period spanning 15 years reported the occurrence of AE in 23 (66%) out of 35 cases of EACs.

About 2% of women with endometriosis have lesions that reportedly undergo malignant transformation [63,64]. Typically, malignant transformation of endometriosis may result in endometrioid adenocarcinoma and clear cell carcinoma, as well as, Müllerian-type mucinous and serous borderline tumors, and adenosarcoma and endometrial stromal sarcoma [63]. Available epidemiological studies also indicated that women with endometriosis may be at a higher risk of extra-ovarian cancers, for example, non-Hodgkin's lymphoma, brain tumors, endocrine cancer, breast cancers, and cutaneous melanoma [65-68]. Figures 4 and 5 summarize the estimated effect sizes reported in various studies on association between endometriosis and ovarian or extra-ovarian cancers. However, we need to acknowledge that several factors might not be taken into account in many epidemiological studies, which included (i) publication bias towards positive associations, (ii) the influence of the phenotype of the disease (e.g., superficial endometriosis, ovarian endometrioma, adenomyosis, or deep endometriosis), (iii) the effects of fibroids, which are often associated with endometriosis, and importantly (iv) the influence of medical treatment and surgery. Furthermore, untoward bias generated from the fact that (i) there may exist common risk factors between OE and OC, (ii) there may occur misclassification due to poorly characterized outcome analysis, and (iii) the known and unknown systemic and behavioural consequences of endometriosis may influence the onset of OC. These issues have been elegantly addressed elsewhere [67,69].

Table 1: Theories of endometriosis.

Developmental stage	Trigger	Description	Author, Year [Reference number]
Predisposition			
	Genetics	Genetic linkage studies indicated higher prevalence of endometriosis in population having first degree relatives afflicted with endometriosis. QTL mapping has traced endometriosis to different chromosomal loci in different studies belonging to different geographical locations. Despite evidence of genetic predisposition, there is no specific loci to which endometriosis can be linked.	Kennedy et al. 1995 [13]; Bischoff and Simpson 2000 [14]; Montgomery et al. 2008 [15]
	Stress	In utero and environmental stressors have been shown to be responsible for endometriosis.	Missmer et al. 2004 [16]; Upson et al. 2014 [17], 2015 [18]; Gao et al. 2019 [19]
	Retrograde menstruation and implantation	According to this theory, the reflux of endometrial effluents during menstruation travel to the peritoneal cavity, and adhere to ectopic sites, causing deposits of endometriosis.	Sampson 1927 [8]
	Coelomic metaplasia and embryonic rest	Endometriosis is caused by transformation of coelome or peritoneum consistent with the putative 'secondary mullerian system'. Endometriosis in MRKH syndrome of uterine agenesis may arise from coelomic metaplasia.	Iwanoff 1898 [20]; Meyer 1924 [12]; Lauchlan 1972 [21]; Signorile et al. 2009 [22]; Konrad et al. 2019 [23]
	Stem cell/ Progenitor cell	Endometrial and bone marrow derived stem cells putatively migrate to ectopic sites and contribute to endometriosis. Potential role of endometrial stem/progenitor cells during thelarche may establish endometrial ectopic lesions.	Sasson and Taylor 2008 [24]; Gargett et al. 2014 [25]; Hufnagel et al. 2015 [11]
	Chimerism	Fetally derived cells in mother's body share many features with hematopoietic stem cells that may differentiate and contribute to endometrial structures in transplant recipients and their survival at ectopic sites. Male microchimerism in eutopic endometrium of endometriosis may play a contributory role. Presence of coding and non-coding genes of MSY origin especially high in EE of infertile women, and even higher in infertile women with OE.	Haig 2014 [26]; Bhat et al. 2019 [27]
	Intrinsically aberrant eutopic endometrium	Intrinsic anomalies in endometrial cells allow their implantation and survival at ectopic sites on retrograde menstruation.	Ulukus et al. 2006 [28]; Liu and Lang 2011 [29]; Brosens et al. 2012 [30]
Progression			
	Hormonal factors	Endometriosis is associated with higher estradiol responsiveness and progesterone resistance leading to increased cell proliferation, reduced secretory differentiation along with inflammatory properties, epithelial-mesenchymal transition, migration and increased survival.	Burney and Giudice 2012 [31]; Andersen et al. 2018 [32]; Bulun et al. 2019 [33]

	Persistent inflammation	Chronic and persistent local inflammatory microenvironment helps sustain growth and maintenance of endometriosis through endometrial-peritoneal adhesion, proliferation, invasion and angiogenesis. Patients with pelvic inflammatory disease display 3-fold higher risk of developing endometriosis.	Suryawanshi et al. 2014 [34]; Lin et al. 2018 [35]
	Immune dysfunction	Altered balance of immune mediators allow cells at ectopic niches to escape immune surveillance.	Lebovic et al. 2001 [36]; Ahn et al. 2015 [37]; Cho et al. 2018 [38]
	Oxidative stress	Imbalanced oxidants and anti-oxidants resulting in oxidative stress is associated with the pathogenesis of endometriosis. ROS causes lipid peroxidation, leads to autophagy and DNA damage.	Van Langendonck et al. 2002 [39]; Scuterio et al. 2017 [40]; Yang et al. 2017 [41]

EE: Eutopic Endometrium; MRKH: Mayer-Rokitansky-Küster-Hauser; MSY: Male-Specific region of the human Y chromosome; OE: Ovarian Endometriosis; QTL: Quantitative Trait Locus; ROS: Reactive Oxygen Species.

Figure 3: Histopathological features of atypical endometriosis (AE). Endometrioma with moderate atypia characterized by mildly stratified epithelial lining and micropapillary tufts seen at low magnification (A), further revealing eosinophilic and clear cell appearances in epithelial lining at higher magnification (B). Endometrioma with severe atypia is characterized by large nuclei with marked pleomorphism, decreased volume ratio of cytoplasm-to-nucleus, cellular stratification and hyperplasia (C).

Figure 4: Forest plot showing effect sizes of EACs retrieved from thirteen (13) individual studies measured in odds ratio (OR), standardized incidence ratio (SIR), relative risk (RR), or adjusted hazard ratio (aHR). The 95% confidence interval (CI) is represented by the horizontal line, and the dimensions of the boxes are proportional to the sample size. Additional studies are also reported in the text.

Figure 5: Forest plot showing effect sizes of EACs in meta-analysis reported in five (5) reviews in terms of summary relative risk (SRR). The 95% confidence interval (CI) is represented by the horizontal line, and the dimensions of the boxes are proportional to the sample size. Additional studies are also reported in the text.
*primarily based on Brinton et al. [85].

Ovarian cancers

In a recent two-center based study on 1000 patients with advanced endometriosis, 20 cases of endometriosis-associated ovarian cancers (EAOC) could be identified, among which endometrioid cancer was reported to be the most frequent (60%), while clear cell carcinoma and serous and mucinous adenocarcinomas were much less frequent (20%) [86]. A large per cent (60 - 80%) of EAOC reportedly occur in the presence of AE [34,58,87-89]. Czernobilsky and Morris [56] observed 43 out of 194 cases of OE showing reactive epithelial changes, four (4) cases of adenomatous hyperplasia and seven (7) cases of severe AE of which one had additional feature of adenomatous hyperplasia. While several AEs in OE may be of reactive origin due to inflammation and regeneration, the possibility that some instances of severe AEs indeed reflect neoplastic potential requires further examination. LaGrenade and Silverberg [90] presented nine (9) cases in which ovarian neoplasms were either associated or contiguous with AE. Further, four (4) cases of extra-gonadal malignancy were noted along with or after detection of AE. They concluded that a diagnosis of AE might be followed by long-term close and careful observation of the patient so that subsequent development of neoplasia, if any, can be detected at the earliest time point. Sainz de la Cuesta et al. [91] based on histological studies of samples obtained from 79 patients with epithelial ovarian cancer confined to only ovaries

(i.e., stage I as per FIGO staging system) observed that 22 patients with endometriosis had 41% endometrioid, 32% clear cell, 9% other types along with the evidence of transition from benign endometriosis to malignancy as revealed from the display of hyperplastic and atypical characteristics. Van Gorp et al. [92], in a large scale review, reported the detection of atypia in about 8% of endometriomas. The occurrence of AE which may be considered as a premalignant precursor with subsequent development of neoplasia was observed in up to 3% of cases of endometriomas by Vercellini et al. [64]. Based on available reports, it appears that endometrial AE and neoplasm occur in OE with an average of 3 out of 5 cancers being clear cell type cancer and 2 being endometrioid cancer and rare incidences of serous and mucinous carcinomas.

15% - 50% of clear-cell and endometrioid ovarian tumors bear association with endometriosis and 2-3 fold increase in the risk of OC reportedly occur in individuals with endometriosis [93-95]. Several lines of evidence indicated that some endometriotic lesions may lead to clear cell and endometrioid OC [67,70,75]. In a large study based on 7911 cases of invasive OCs reported by the Ovarian Cancer Association Consortium, self-reported history of endometriosis was observed to be strongly associated with risk of EAOCs [54]. Based on data obtained from large prospective cohort with 18 year follow-up study of self-reported endometriosis, Poole

and colleagues [78] reported an association with OC with relative risk (RR) of 1.81, while stronger association was observed for laparoscopically-confirmed endometriosis with RR of 2.14.

There has been an indication in a few reports that patients of EAOC generally had a lower stage of cancer, and significantly better prognosis and overall survival as compared with other OCs [96,97]. A possible explanation for such an observation is that benign symptomatic disease is often associated with increased number of administration of examinations and scans, resulting in earlier diagnosis [95]. In fact, women with EAOC are generally diagnosed at an earlier stage and with low-grade disease [48,98]. On the other hand, endometriosis *per se* did not appear to predict prognosis especially in clear cell and endometrioid tumors, and not result in better overall survival in a separate study [99]. Paik et al. [77] did not observe any significant differences in survival data between EAOC and non-EAOC, suggesting that cancer arising from endometriosis did not have better prognosis.

Finally, whether the reported association between endometriosis and ovarian cancer is indeed suggestive of any causal relationship can be debated as such association might be reflective of the fact that these two clinical entities share common risk factors [46]. Indeed, endometriosis and ovarian cancer may share some common risk factors, for example early menarche, repeated ovulatory menstrual cycles and stress, and protective factors, for example tubal ligation, hysterectomy, oral contraception and physical activity [69].

Endometriosis-associated extra-ovarian cancers

A recent study on the world-wide assessment of endometrial cancer and its risk factors revealed endometrial cancer as the sixth most common neoplasm in women [100]. This study documents remarkable increase in endometrial cancer (EC) in 26 of the 43 populations studied during 1978-2013. The age-period-cohort analysis revealed in fact largest increases prevalent in South Africa and in several Asian countries (Japan, the Philippines, Singapore, and India) and in Belarus, Lithuania, Costa Rica, and New Zealand [68]. The histologic subtypes of cancer arising from the endometrium closely mirror the types found in the ovary; also the epidemiology of OC and EC is apparently closely entwined [101]. The most standardized classification divides EC into two different subtypes: endometrioid carcinomas (type I), and non-endometrioid carcinomas (type II); type I is the frequent,

less aggressive subtype, while type II generally display more aggressive phenotype [102].

While there appears to exist a moderately significant association between endometriotic lesions and the onset of OCs, it is not apparent whether endometriosis is indeed a risk factor in the development of EC. In fact, epidemiological studies in establishing a link between a diagnosis of endometriosis and risk of EC provide somewhat conflicting evidence. Poole et al. [78] reported that endometriosis was not associated with a risk of EC largely corroborating earlier data that endometriosis as a risk factor for EC was inconclusive [103]. On the other hand, another large cohort study conducted by Mogensen and colleagues [75] on 45,790 women with a clinical diagnosis of endometriosis during 1977-2012 from the Danish National Patient Register and the Danish Cancer Register revealed that endometriosis besides being an increased risk for OC bears higher risk for EC, primarily of type I. A population-based retrospective cohort study has further identified an association between endometriosis and EC developing in the later life [104]. Furthermore, in a case-control study using self-reported endometriosis cases, endometriosis was observed to be a risk factor for OC or EC patients between the age of 40 and 85 [72]. An association between a previous diagnosis of endometriosis and risk of EC appeared real from a multi-model study [105]. Finally, in a meta-analysis of 32 studies published between 1989 and 2018 reporting on the risk of extra-ovarian malignancies among women with endometriosis, a significant risk of EC was recorded [84].

Among other extra-ovarian cancers, higher vulnerability to breast cancers in women with endometriosis, especially in the later life is noteworthy [106-110]. However, a large scale survey of 766,556 person-years revealed an increased risk of non-Hodgkin's lymphoma, brain tumors, and endocrine cancer besides OC but with no significantly increased overall risk of EC and breast cancer as compared to the general population [65].

In general, conclusions derived from epidemiological studies should be interpreted with utmost caution for various reasons. Inadequate operative confirmation of endometriosis, and lack of uniformity in data reporting as well as study design, insufficient information regarding range of data heterogeneity and adjustment for confounding factors are most impactful [111,112]. Kvaskoff et al. [67] although observed an overall increasing evidence to suggest that endometriosis patients are

at higher risk of several chronic diseases, commented that certain methodological complexities that are not generally considered should indeed be addressed in such association studies: (i) temporality in the diagnosis and progression of endometriosis and of cancer, (ii) misclassification of endometriosis (self-reported and/or laparoscopically diagnosed), (iii) whether associations are driven by common risk factors, and (iv) the stage and the subtype of endometriosis. Thus, due stringency must be imposed while interrogating prior to arriving at any conclusion regarding any meaningful association between ovarian endometriosis and the onset of ovarian cancer [46].

While the assumption that untreated and unmanaged endometriosis may predispose women to OC appears valid, the underlying causal molecular links are not clearly defined. The question whether OCs with and without concurrent endometriosis develop through common pathogenetic pathways also requires attention. These issues shall be discussed in the following sections.

Molecular basis of endometriosis-associated cancer

Cancers are typically known to depend on mutations in critical genes that confer a selective advantage to the tumor cell. The groups of such critical genes that harbor the *driver* mutations contributing to the disease process either act as 'oncogenes' or 'tumor suppressors'. Oncogenes or proto-oncogenes normally help cells grow within physiological limits, but with mutation and/or unregulated activation, those genes become oncogenic and can lead to cancer. Tumor suppressor genes normally slow down cell division, repair DNA mistakes, or instruct cells when to die via apoptosis; but when they are inactivated it can lead to cancer. Some genes though may have both oncogenic and tumor-suppressor functions, referred as *proto-oncogenes with tumor suppressor functions* which include a large number of transcription factors and kinases; Tumor protein 53 (*TP53*) occupies an important position in the list [113]. Attention is also being focused on microRNAs (miRNAs) which are a class of small noncoding regulatory RNAs with 19–25 nucleotides and post-transcriptionally regulate gene expression, primarily through inhibitory regulation of translation but they may also enhance translation. In the following section, we shall focus our attention on the putative role of some of these genomic cues which are potentially involved in EACs.

Oncogenes and tumor suppressor genes

Multifocal endometriotic lesions are clonally related and carry considerable burden of mutation towards development of neoplasm [114,115]. As detailed in table 2, mutations resulting in repression of specifically three (3) tumor suppressor genes like *ARID1A*, *PTEN* and *TP53* and mutations resulting in over-activities of *KRAS*, *PIK3CA* and *PPP2R1A* have been reported to be commonly associated with endometriosis, as well as, with OCs [48,116]. Iranzo et al. [117] have identified four major genomic modules in the subnetwork of gynecological cancers, of which module II and module IV specifically could be detected in about 60% of endometrial and uterine cancer cases. Interestingly, many of the genes of module II and module IV are represented in EE and ET as shown in figure 6.

Figure 6: A pie map of genes expressed in endometrial tissue in EE and ET belonging to module II and module IV of four major genomic modules in the subnetwork of gynecological cancers. About 60% of endometrial and uterine cancer cases show association with these two specific modules. In others category, genes belonging to modules I (CBFB, CDH1, GATA3, MAP2K4, MAP3K1, PIK3CA, RUNX1, TBL1XR1, TBX3) and III (FOXA1, SPOP) are included, which are reportedly present in 2% endometrial cancers and under-represented in EE and ET. Source: Previs et al. [116], Iranzo et al. [117].

Stamp et al. [62] observed 66% cases of EAC had AE with 6 out of 10 cases of AE showing loss of BAF250a which is a nuclear protein that governs chromatin remodeling, and mutations in *ARID1A*; in 8 cases of AE not associated with cancer there was no loss of BAF250a. The loss of *ARID1A* in 10/25 (40%) uterine endometrioid carcinoma cases along with 15/58 (26%) loss of *ARID1A*

immunoexpression led Guan et al. [135] to suggest that the molecular basis of pathogenesis of low-grade uterine endometrioid carcinoma is comparable to that of low-grade OCs. Additionally, aberrant activation of *CTNNB1* due to its mutation affect the expressions/activities of *c-MYC*, *PTEN/PI3K*, and this appears to be a crucial step in the progression of several cancers including OCs and ECs and this functional network has been implicated in endometriosis as well [145-152].

Recent experimental studies using mouse model substantiate the involvement of subnetwork of the above modules in the progression of endometriosis and EAO. Dinulescu and colleagues [153] could successfully develop an experimental mouse model of PE and ovarian endometrioid carcinoma by the expression of oncogenic *Kras* or conditional *Pten* deletion within the ovarian surface epithelium that resulted in pre-neoplastic ovarian lesions with endometrial glandular morphology. The combinatorial effect of mutations of both genes in the ovary resulted in endometrioid ovarian adenocarcinomas [153]. In a transgenic mouse model of OC, malignant transformation in endometriosis with mutation of *Kras* and *p53* deletion within the ovarian surface epithelium showed hyperproliferative endometrioid glandular morphology [154]. Endometrial endometrioid cancer (EEC) may be developed in a mouse model by the concurrent involvement of loss of function in *PTEN*, gain of function of *PI3K* and *CTNNB1* [155].

In general, both clear cell and endometrioid OCs commonly display highly frequent mutations in *ARID1A*, *CTNNB1*, *KRAS*, *PIK3CA* and *PTEN*, irrespective of associated endometriosis [156]. McConechy et al. [157] however in a study of the mutation profiles of EEC and EAO (morphologically similar tumors) have reported differences in *PTEN* and *CTNNB1* profiles. Low grade EECs show 67% *PTEN* and 27.5% *CTNNB1* mutations, while in EAOs there was 16.6% *PTEN* and 53.3% mutations in *CTNNB1* with no significant differences in the mutational frequencies of *ARID1A*, *PIK3CA*, *PPP2R1A* and *TP53*. It is likely that the inflammatory and oxidative-environmental niche during oncogenesis may be reflective of such distinct mutation patterns observed in EEC as compared to EAOs. While it is plausible that persistent inflammatory niche at ET lesion may cause genetic and epigenetic changes specific to EAOs [97,158], the question whether OCs with and without concurrent endometriosis develop through common pathogenic pathways remains unsettled due to the fact that a large number of women with EAOs do not have endometriosis at the time of staging and 1 out

of 3 patients with endometrioid or clear-cell OCs show concurrent endometriosis [156]. Also, studies often fail to report whether endometriosis is present with concurrent AE, absence of which may give erroneous construction of such an inference.

Furthermore, how two most common OCs (i.e., clear cell and endometrioid) with distinctive differences in their morphological as well as immunohistochemical characteristics, and responses to chemotherapy arise from endometriosis is not clear. Despite some genes are more commonly mutated in endometrioid OCs (e.g., *CTNNB1*), while others in clear cell OCs (e.g., *PIK3CA*, *ARID1A*), there is no robust and specific genetic signature either for endometrioid OCs or for clear cell OCs [159,160]. Cochrane et al. [161] demonstrated that endometrioid OCs were derived from cells of secretory cell lineage, whereas clear cell carcinomas were derived from ciliated cell lineage, suggesting that differences in endometrioid OC and clear cell OC are attributable to distinct cells of origin. Collectively, the different histologic subtypes of OCs arising from endometriotic lesion may reflect the interlacing of specific cues from cells of differential origin and their specific responses due to the effects of genetic, epigenetic, hormonal and stress related factors on those cells in the tumor microenvironment [162,163].

It is notable in this regard that mutations in cancer-associated driver genes alone may not be sufficient for malignant transformation. Mutations in cancer somatic driver genes, *ARID1A*, *PIK3CA*, *KRAS* and *PPP2R1A* were detected in 26% (10/39) epithelial cells of DIE which is an endometriosis subtype with little risk of malignant transformation. One patient of DIE harbored an identical *KRAS* mutation in three distinct DIE lesions and also in normal sampling of EE and endocervical epithelium [164]. Similarly, Suda et al. [126] observed mutational landscapes of *KRAS* in 38% and of *PIK3CA* in 29% of subjects with OE and mutations (mutated in >5% samples) of *PIK3CA* and *KRAS* were identified in epithelia of normal endometrium. The 'driver genes' like *ARID1A*, *PIK3CA*, *KRAS*, *PPP2R1A* and *TP53* are reportedly present in benign, nonmalignant settings and thus the issue of oncogenicity needs to be considered in tissue context-dependent manner [165]. Guo [166] suggests that a web of gene expressions anchored by the set of driver genes, (e.g. *TP53*, *PTEN*, *ARID1A*, *PIK3CA*, *KRAS* and *PPP2R1A*, *CDKN2A*, *NF2* and *NOTCH1*) are likely to be involved in inducing EMT and progressive fibrogenesis in ET lesions. Cyclic bleeding associated with inflammatory and oxidative stress followed by subsequent tissue repair similar to that occurring in EE may be viewed as

wounds that undergo repeated tissue injury followed by repair along with recurrent estrogenic stimulation and ovulatory events which in the pelvic environment lead to smooth muscle metaplasia (SMM) and fibrogenesis associated with epithelial-mesenchymal transition (EMT) and fibroblast-to-myofibroblast trans-differentiation (FMT), and tumorigenesis especially in high risk patients [166-169].

The question whether EE of women with endometriosis bearing intrinsic anomaly as evidenced by alterations in its immune system [170,171], critical number of EE cells with stem cell characteristics [11, 111] and having epigenetic modifications [172] may contribute to the development and progression of endometriosis warrants investigation. In a study of selected tumor suppressor and oncogenes in EE and autologous ET lesions obtained from women with ovarian endometriosis, Laudanski et al. [118] observed higher levels of oncogene *AKT1* and tumor suppressor gene product *4EBP1* mRNAs and their protein expressions in EE of women with endometriosis compared with control patients suggesting up-regulation of *AKT1* and *4EBP1* in EE might be associated with the pathogenesis. Khan et al. [130] in a study of genome-wide expressions in autologous EE and ET of fertile women with endometriosis observed that EE in severe stage ovarian endometriosis was transcriptionally dysfunctional in mediating immune-neuro-endocrine responses with vulnerability to give rise to ET lesion through a pathways network of *CLOCK-ESR1-MYC*. Although a few genes (*CHEK1*, *ERBB* family, laminin gamma and Ki-67) associated with gynecological cancers [130] were highly expressed in autologous, paired EE and ET, however, several groups observed a lack of overt oncogenic potential in EE and ET [130,173-175]. It appears plausible that developmental process of unmanaged and untreated endometriosis induces oncogenic transformation in the lesion sites primarily in the high risk population [95,176-178]. It is noteworthy that whole-exome sequencing of endometriosis revealed unique mutational signature in ET *versus* EE, with no overlap in somatic single nucleotide variants [114]. Such mutually exclusive mutations occur, presumably because of the discrepancy in endometriosis pathophysiology in EE *versus* ET.

Potential involvement of miRNA

MicroRNAs (miRNAs) are small non-coding RNAs and are involved in various physiological and pathophysiological processes like embryogenesis, development, differentiation, proliferation, cell metabolism, cell-cell communication, cell survival, apoptosis, immune

response, and oncogenesis [179]. MicroRNAs play an important role in the initiation, progression and metastasis of OCs and may serve as potential emerging biomarkers of endometriosis [180]. Table 3 highlights the profiles of miRNAs in EE and ET of women with and without endometriosis and in EACs and their putative functional roles.

The issue of miRNA in endometriosis has been earlier elaborated in several reviews [178,182,207,208]. Several groups earlier reported a group of specific miRNAs that were differentially displayed between EE and ET, and between CE and ET [209-212]. Although there are quite a few differentially expressed miRNAs in endometriosis so far reported, further studies are required to identify miRNAs which may modulate critical elements in biological pathways which are highly significant for the pathophysiology of endometriosis including cellular proliferation, invasion, EMT and angiogenesis. In this line, it is noteworthy that a meta-analysis of 12 studies on miRNA profiling that were conducted in patients from China, Italy, Poland, Spain and USA revealed down-regulated miRNAs (e.g., miR-200 a,b,c, miR-15b, miR-106b, miR-15b, miR-141, miR-150, miR-196 and miR-375) and upregulated miRNAs (e.g., miR-1, miR-150, miR-202, and miR-365) in ET and EE as compared to CE, which were enriched in cancer, Wnt signaling pathway, and angiogenesis [213].

Table 4 provides a list of common miRNAs which are upregulated or down-regulated in ET and EACs as compared to CE or EE. Several studies reported about various miRNAs having differential expression in OCs [178,214-216]. Of various miRNAs showing association with ET and EACs, specifically a few have drawn serious attention as addressed below.

- Let-7: Lethal (let)-7 family is comprised of tumor suppressor miRNAs, and involved in several kinds of tumors [217]. Let-7i expression was observed to be markedly reduced in tumors of cancer patients with poor survival and in chemotherapy-resistant patients with OC [218].
- miR-200 family: MiR-200s are functionally involved in EMT, epithelial cell polarity, and cancer metastasis [219]. Four (4) members of miR-200 family (miR-200a, miR-141, miR-200c, and miR-200b) were seen to be upregulated in OCs compared with ET [220]. On the other hand, the expression levels of different members of miR-200 family were differentially associated with the specific histotypes of OCs. For

example, over-expression of miR-200a and miR-200c occurs in serous, endometrioid and clear cell OCs, whereas miR-200b and miR-141 were upregulated in endometrioid and serous histotypes, not in clear cell OCs [220].

- miR-191: MiR-191 expression is reportedly higher in both endometriosis and EAOs and its expression was observed to be negatively correlated with TIMP3 which is a proapoptotic protein [203,221]
- miR-126: MiR-126 is commonly down-regulated in ET and EAOs compared with EE and generally considered as a predictor of poor survival of cancer patients [222,223]. miR-126 targets on KRAS, PI3K and VEGF and its down-regulation is associated with proliferation, migration and invasion [224].
- miR-34 family: Dysregulated miR-34 has reportedly been associated with EE, ET and EAC, presumably due to its targets on transcript subnetworks toward regulation of cell proliferation, migration and invasion [181,182,184,185]. Dysregulated miR-34 is frequently associated with aberrant activities of *TP53*, *c-MYC* and *CNNB1*, all which have been implicated in endometriosis and EACs [183].

Generally, available evidence suggests that miRNAs are dysregulated in ectopic lesion sites putatively contributing to the pathogenesis of the disease and trigger the developmental process of oncogenesis. Future studies are required to define the roles of the dysregulated miRNAs in endometriosis pathophysiology and progression to EAOs by identifying the pathways and their components that are regulated by these miRNAs. Studies are warranted to understand the pathophysiological basis of EAO and for the discovery of diagnostic bio-markers. Finally, epigenetic modifications in terms of alterations in the DNA methylation pattern and chromatin remodeling have been associated with development of endometriosis and EAO; several groups have elaborated upon this issue [137,178,225,226]. Additionally, it will be of interest to understand the basis of the greater risk of gynecological cancers among infertile women affected by endometriosis [85,227,228]. It is important that the impact of heterogeneities at level of tissue, disease and histotypes, and other context-specific determinants are considered with due weightage while undertaking such studies in the future [229]. Several groups have further suggested that studies using models of phylogenetic parsimony may provide an answer to the related questions, as it has already been done for metastatic prostate cancer [46,230,231].

Conclusion

Women with unmanaged and untreated endometriosis are at a modestly increased risk for the development of carcinomas of the ovary and uterus with time. Figure 7 depicts the schema of a proposed model providing imageries of how endometriosis may be driven to malignant potential. As shown, *driver modules* are the key components of biological pathways that are highly relevant to the pathophysiology of endometriosis as these regulate the underlying pathophysiological processes including cellular proliferation, cell survival, EMT, and angiogenesis, which may lead to fibrosis. Further studies are therefore required to identify the *drivers* that modulate key events conducive to the pathophysiology of ovarian cancers from ectopic lesions via atypical endometriosis and the *passengers* that may change as a result of the disease pathogenesis.

Collectively, it appears that multifocal endometriotic lesions are clonally related and carry significant mutational burden and those endometriotic lesions carrying sufficient cancer-associated mutations are to be considered neoplasms themselves with cognizable malignant potential. Nevertheless, further research is needed for delineating the precise causative hallmarks of EAO and for profiling OE as a risk factor since several studies had indeed failed to meaningfully substantiate these issues. It is to be noted in this regard that the fundamental hallmark of cancer, namely genomic instability is not typically found in endometriosis.

Despite the fact that the risk of OC in endometriosis is only modest, we believe that the cases of OE depending on clinical details may be pragmatically taken in view of the patient's care as a pre-malignant field defect keeping Knudson's two-hit theory in perspective. We propose that women diagnosed with atypical endometriosis should be referred to a gynecologic oncologist for deeper investigation using molecular approaches and for specific gynecological management as a part of the SOP for endometriosis management, for a high-risk vulnerable population as summarized in figure 8.

Table 2: Common driver oncogenes and tumour suppressor genes associated with endometriosis and endometriosis-associated cancer.

Gene name	Relevant observations and references
<i>Oncogenes</i>	
<i>AKT1</i>	<p>AKT1 is an oncogene. AKT/PKB (protein kinase B) kinases, which include AKT1, AKT2, and AKT3, are key intermediates of signaling pathways that regulate cellular processes controlling cell size and growth, proliferation, survival, glucose metabolism, genome stability, and neo-vascularization. Via PI3K-dependent phosphorylation and activation of serine/threonine kinase AKT mediates a key activator of cell survival mechanisms. AKT relieves the negative regulation of mTOR to activate protein synthesis and cell proliferation through 4EBP1.*</p> <ul style="list-style-type: none"> • Higher AKT1 and 4EBP1 mRNA in EE vs CE. Higher 4EBP1 in paired EE vs ET but no change in AKT1 protein in ET vs CE [118]. • Overactivation of the phosphatidylinositol 3-kinase/AKT signaling pathway led to reduced expression of IGFBP1 through reduced levels of nuclear FOXO1 in ET compared with CE. MK2206, an allosteric AKT inhibitor increased accumulation of nuclear FOXO1 and IGFBP1 expression [119]. • High levels of pAkt immunostaining in stromal and glandular cells in EE and ET in endometriosis compared with CE during early secretory phase [98,120]. • Secretory phase EE of endometriosis with cell proliferation linked to deregulation of c-kit/SCF-associated signaling pathways along with over-expressed pAkt and pGSK3b in proliferative and secretory phases of menstrual cycle [121]. • Enhanced phosphorylation of Akt, higher Bcl2, MMP2 and MMP9 along with higher CCL19 and CCR7 in EE with endometriosis and in peritoneal fluid compared to CE putatively promoted endometrial stromal cell proliferation and invasion [122].
<i>KRAS</i>	<p>KRAS is a driver oncogene for OC and acts as an on-off switch in cell signaling. It controls cell proliferation, and its mutational over-activation can cause cells to continuously proliferate and often develop into cancer.*</p> <ul style="list-style-type: none"> • Variant KRAS with polymorphism in a let-7 miRNA binding site in the 3'-UTR of KRAS was detected in 31% of women with endometriosis. Higher KRAS mRNA and protein expression was observed in endometrial stromal cells in-vitro of women bearing the KRAS variant with increased cell proliferation and invasion [123]. • KRAS mutations identified in 29% (12/42) of endometriosis-associated endometrioid adenocarcinomas, but only in 3% (1/29) tumors not associated with endometriosis suggesting KRAS mutations may play a role in the development of endometriosis-associated adenocarcinoma [124]. • EE from women with endometriosis shows coordinated activation of KRAS and over-expression of Sirtuin 1 (SIRT1), a histone deacetylase and gene silencer throughout the menstrual cycle [125]. • Multiregional sequencing show unique mutational landscapes of KRAS in 38% of subjects in ovarian endometriotic epithelium, while KRAS mutations (mutated in >5% samples) identified in epithelia of normal endometrium as well [126].
<i>MYC</i>	<p>MYC is an oncogene which plays pivotal function in the control of cellular growth and differentiation and apoptosis.*</p> <ul style="list-style-type: none"> • Detected in EE and ET cells of endometriosis suggestive of its role in cell proliferation [127]. • Case report of EAOA arisen in endometriotic cyst evaluated for genomic instability by comparative genomic hybridization revealed a gain of 8q, including the locus of c-MYC at 8q24 with higher immunoexpression of c-MYC, p53 and cyclin D1 in EAOA as compared to endometriotic cyst [128]. • EE and ET of infertile endometriosis express significantly higher c-MYC mRNA and protein in proliferative phase with higher Ki67 immunostaining, apoptosis in ET with lower Bax mRNA in secretory phase compared with CE [129]. • Dysregulation of MYC along with CLOCK and ESR1 major transcription factors observed in OE stages III-IV in EE and ET of fertile women [130]. • c-MYC mRNA higher in ET, and higher protein in EE and ET of endometriosis compared with CE with concomitant higher ERA and ERB mRNA in ET [131]. • Protein expressions of MYC and TWIST1 in ectopic tissue upregulated in glandular epithelium which are involved in EMT, whereas stromal MYC expression was down-regulated [132].

<i>PIK3CA</i>	<p>PIK3CA is an oncogene which is an integral part of the PI3K pathway.*</p> <ul style="list-style-type: none"> • Somatic mutations of PIK3CA gene detected in 43% (10/23) clear cell OC in the kinase domain. Identical mutation detected in 90% (9/10) coexisting endometriotic epithelium adjacent to clear cell OC and in 6/9 ET without atypia. The mutation of PIK3CA gene may be associated with the malignant transformation of endometriosis [133]. • Multiregional sequencing revealed unique mutational landscapes of PIK3CA in 29% of subjects in ovarian endometriotic epithelium and PIK3CA mutations (mutated in >5% samples) along with KRAS was identified in epithelia of normal endometrium [126].
<i>Tumor suppressor genes</i>	
<i>ARID1A</i>	<p>ARID1A is a tumor suppressor gene that encodes BAF250 protein that interacts with ATPase subunits to form the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex.*</p> <ul style="list-style-type: none"> • ARID1A mutation occurs in clear-cell and endometrioid OC but not in serous carcinoma. ARID1A mutation and loss of BAF250 detected in tumor sites and in contiguous atypical endometriosis suggestive of an early event in the transformation of endometriosis into cancer [134]. • ARID1A loss detected in 10 (40%) of 25 uterine endometrioid carcinoma, while none of 12 uterine serous carcinomas and none of 56 ovarian serous and mucinous carcinomas harbored somatic ARID1A mutations. Immunoexpression of ARID1A loss detected in 15 (26%) of 58 cases suggesting that the molecular pathogenesis of low-grade uterine endometrioid carcinoma is similar to that of low-grade endometrioid and clear cell OC [135]. • ARID1A mRNA and protein loss in ET and in EAOC associated with reduced expression for antioxidant, Mn-SOD and high levels of malondialdehyde indicative of oxidative stress [136]. • Down-regulation of ARID1A mRNA associated with higher promoter methylation level of ARID1A and associated upregulated DNMT1 gene and protein expressions in ET compared with CE [137].
<i>PTEN</i>	<p>PTEN a tumor suppressor gene encoding a phosphatase that dephosphorylates phosphatidylinositol-3,4,5-triphosphate interfering with its function to inhibit cell death mediated by protein kinase B and to encourage cell proliferation.*</p> <ul style="list-style-type: none"> • PTEN loss detected immunohistochemically in 19% benign EE vs 55% in EC [138]. • Loss of heterozygosity (LOH) at locus 10q23.3 of PTEN detected in 13/23 solitary endometrial cysts (56.5%), 8/19 endometrioid OCs (42.1%) and in 6/22 clear cell OCs (27.3%). Somatic mutations in PTEN gene identified in 7/34 solitary endometrial cysts (20.6%), in 4/20 endometrioid OCs (20.0%) and in 2/24 clear cell OCs (8.3%). LOH at the 10q23.3 locus, PTEN somatic mutations and changes in the levels and distribution of proteins in the PTEN-PI3K/Akt signal transduction pathway are associated with endometriosis. Inactivation of the PTEN gene appears as an early event in the development of endometrioid and clear cell OCs [139,140].
<i>TP53</i>	<p>TP53 was the first tumor suppressor gene to be identified. It regulates the cell cycle and functions to prevent cancerous cell growth. The tumor suppressor p53 protein known to play a critical role in different cellular processes in response to DNA damage is responsible for transcriptional induction of the p21 gene. Both p53 and p21 are thought to play major roles in the development of human malignancy.*</p> <ul style="list-style-type: none"> • Somatic p53 locus alterations has been associated with the pathogenesis of late- or severe-stage endometriosis [141]. • Polymorphism of p53 codon 72 may be involved in the development of endometriosis in a study of Taiwanese population [142]. • p53 SNPs are not associated with endometriosis in Indian women. However, LOH and reduced expression of p53 are related with the risk of endometriosis in Indian women [143]. • p53 is significantly down regulated in ET compared to EE and CE [144].

*Source: <https://www.ncbi.nlm.nih.gov/gene/>

ATPase: Adenosine Triphosphatase; 4EBP1: Eukaryotic translation initiation factor 4E Binding Protein 1; AKT1: AKT serine/threonine Kinase 1; ARID1A: AT-Rich Interaction Domain 1A; BAF250: Barrier to Autointegration Factor; Bcl2: B-Cell Lymphoma 2; Bax: Bcl-2-Associated X protein; CCL: Chemokine Ligands; CCR: C-C motif Chemokine Receptor; CE: Control Endometrium; CLOCK: Clock circadian regulator (Circadian Locomotor Output Cycles protein Kaput); DNMT1: DNA Methyltransferase 1; EAOC: Endometriosis-Associated Ovarian Cancer; EE: Eutopic endometrium from proven Endometriosis; EMT: Epithelial-Mesenchymal Transition; ERA: Estrogen Receptor Alpha; ERB: Estrogen Receptor Beta; ESR1: Estrogen Receptor 1; ET: Ectopic Tissue; FOXO1: Forkhead box O1; IGFBP1: Insulin like Growth Factor Binding Protein 1; KRAS: KRAS proto-oncogene, GTPase; Guanosine Triphosphatase; LOH: Loss of Heterozygosity; MMP: Matrix Metalloproteinase; MnSOD: Manganese Superoxide Dismutase; mTOR: Mammalian Target of Rapamycin; MYC: MYC proto-oncogene, bHLH transcription factor; OC: Ovarian Cancer; p21: cyclin-dependent kinase inhibitor 1; pGSK3b: Phosphorylated Glycogen Synthase Kinase 3 Beta; PI3K: Phosphoinositide 3-kinase; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-Kinase Catalytic subunit Alpha; PKB: Protein Kinase B; PTEN: Phosphatase and Tensin homolog; SCF: Stem Cell Factor; SIRT1: Sirtuin (Silent mating type Information Regulation 2 Homolog) 1; SNP: Single Nucleotide Polymorphism; TP53: Tumor Protein p53; SWI/SNF: SWItch/Sucrose Non-Fermentable; TWIST1: Twist basic helix-loop-helix Transcription factor 1; UTR: Untranslated Region.

Table 3: MicroRNAs in endometriosis and endometriosis-associated cancers.

Sample details	Major observations and comments	Author, Year [Reference No.]
<i>Endometriosis-associated studies</i>		
EE and CE; Asian, Caucasian and unknown populations	Dysregulated miR-9 and miR-34 families in early secretory phase EE endometrium suggestive of proliferative fingerprint. Notable that miR-34 targets on transcript subnetworks toward regulation of cell proliferation, migration and invasion and is associated with aberrant activities of TP53, c-MYC and CTNNTB1.	Burney et al. 2009 [181]; Hawkins et al. 2011 [182]; Rokavec et al. 2014 [183]; Corney et al. 2010 [184]; Wang et al. 2017 [185]
ET, EE and CE stromal cells; Japanese population	Reported 12 differentially regulated miRNAs in ET including down-regulated miR-196b. Transfection of cells with miR-196b resulted in suppressed proliferation, apoptosis, c-MYC and Bcl-2 mRNA. Notable that miR-196b acts as a tumor suppressor. Its down-regulation may provide a selective growth advantage to pre-malignant cells.	Abe et al. 2013 [186]; Tellez et al. 2016 [187]
ET, EE and CE; Caucasian population in Spain	Differential miRNA profiles among three tissue types characterized by lower miR-202-3p, miR-424-5p, miR-449b-3p and miR-556-3p along with higher VEGF-A and uPA in ET than CE. Notable that miR-202 inhibits cell proliferation, migration and invasion involving STAT3.	Braza-Boils et al. 2014 [188]; Zhao et al. 2017 [189]; Zhang et al. 2018 [190]
ET, EE and CE; Chinese population	Down-regulated miR-183, miR-215 and miR-363 in ET and EE was associated with suppression of inhibition on invasive ability and apoptosis. Notable that miR-183 may act as a tumor suppressor.	Shi et al., 2014 [191]; Bian et al. 2018 [192]; Yang et al. 2019 [193]
ET and CE; Chinese population	Down-regulated miR-200b, miR-15a-5p, miR-19b-1-5p, miR-146a-5p, miR-200c, and up-regulated miR-106b-5p and miR-145-5p with upregulated VEGF-A, EGFR2, PTEN and CXCR4 in ET. MiR-200c downregulation and upregulation of lncMALAT1 in EE regulates EMT. It is notable that MALAT1 lncRNA promotes metastatic phenotype.	Yang et al. 2016 [194]; Liang et al. 2017 [195]; Du et al. 2018 [196]; Li et al. 2019 [197]
ET and EE; Chinese population	Integrated analysis revealed specific miRNAs as key regulators (miR-34c-5p, miR-200a-3p, miR-141-3p and miR-183-5p) and major targets (miR-449a, miR-449b-5p, miR-449c-5p and miR-196b-5p) in the developmental process of endometriosis.	Zhao et al. 2018 [198]
<i>Endometriosis-associated cancer studies</i>		
CE, HE and EEC	Higher level of expression miR-96 and miR-182 in endometrioid OC. Loss of FOXO1 expression and malignant transformation appeared coinciding with a strong induction of these miRs.	Myatt et al. 2010 [199]; Gutilla et al. 2009 [200]
Clear cell OC with and without coexistent endometriosis	Aberrant expression of miR-21 appears critical in the regulation of PTEN resulting in carcinogenesis.	Hirata et al. 2014 [201]; Wu et al. 2017 [202]

ET, EE and EAOC; ET cell line (CRL-7566) and EAOC cell line (CRL-11731)	Higher miR-191 in ET, highest in EAOC, possibly associated with the regulation of cell proliferation and invasion. Notable that miR-191 may mediate tumorigenic activity of estrogen in ER positive target cells.	Dong et al. 2015 [203]; Tian et al. 2015 [204]
ET and OC, paired; United States	Differentially regulated miRs including down-regulated miR-1, miR-133a, miR-145 and up-regulated miR-200a, miR-200c, miR-141 in OC as compared to ET were associated with reduced PTEN expression with no change in NF-kB in OC as compared to endometriosis.	Wu et al. 2015 [205]
ET, EE and Endometrioid OC; Romanian population	4 miRs over-expressed in endometriosis, 15 miRs differentially expressed in OC. miR-291-a-3p, miR-325-5p, and miR-492 up-regulated in ET and OC compared with EE; miR-200 family overexpressed in OC compared to ET playing a role in EMT. Let miR family having a role in inhibiting activity on oncogenes (KRAS, HRAS, c-MYC and HMG-2) was down-regulated in OC compared to ET.	Braicu et al. 2017 [206]

Bcl-2: B-cell Lymphoma 2; CE: Control (disease-free) Endometrium; CTNNTB1: Catenin Beta 1; CXCR4: C-X-C Chemokine Receptor type 4; EAOC: Endometriosis-Associated Ovarian Cancer; EE: Eutopic endometrium from proven Endometriosis; EEC: Endometrial Endometrioid Cancer; EGFR: Epidermal Growth Factor Receptor; EMT: Epithelial-Mesenchymal Transition; ET: Ectopic Tissue; FOXO1: Forkhead box O1; HE: Hyperplastic Endometrium; HMG-2: High Mobility Group box 2; HRAS: Harvey Rat Sarcoma viral oncogene homolog; GTPase: Guanosine Triphosphatase; KRAS: KRAS proto-oncogene; lncRNA: Long non-coding RNA; Let miRNA: Lethal microRNA; MALAT1: Metastasis Associated Lung Adenocarcinoma Transcript 1; MYC: MYC proto-oncogene bHLH, transcription factor; NF-kB: Nuclear Factor Kappa-light-chain-enhancer of activated B cells; OC: Ovarian Cancer; PTEN: Phosphatase and Tensin homolog; STAT3: Signal Transducer and Activator of Transcription 3; TP53: Tumor Protein p53; uPA: urokinase-type Plasminogen Activator; VEGF: Vascular Endothelial Growth Factor.

Table 4: Common microRNAs in endometriosis and endometriosis-associated ovarian cancers.

Between endometriosis and clear cell ovarian cancers
· Upregulated: miR-125b, miR-143, miR-145, miR-145-5p, miR-191, miR-193a-5p, miR-194, miR-195, miR-223, miR-299-5p, miR-362-5p, miR-365, miR-451, miR-509-3-5p, miR-574-3p, miR-574-5p, miR-628-3p.
· Down-regulated: let-7a, let-7c, miR-106a, miR-106b, miR-126, miR-141, miR-148a, miR-17-5p, miR-182, miR-183, miR-196b, miR-200c, miR-20a, miR-34c-5p, miR-449b, miR-92a, miR-93.
Between endometriosis and endometrioid ovarian cancers
· Upregulated: miR-16-5p, miR-205, miR-30e-5p, miR-325, miR-492, miR-637.
· Down-regulated: let-7f, miR-126.
Between clear cell and endometrioid ovarian cancers
· Upregulated: miR-200a, miR-200c, miR-21, miR-575.
· Down-regulated : let-7d, miR-1, miR-100, miR-101, miR-105, miR-125a, miR-125b-1, miR-126, miR-133a, miR-137, miR-140, miR-143, miR-144, miR-146b-5p, miR-147, miR-199a, miR-199b, miR-222, miR-224, miR-29b, miR-29c, miR-29c*, miR-302a, miR-302b, miR-302c, miR-34b*, miR-9, miR-9*, miR-99a.

Based on Wendel et al. [156]. *miRNA resulting from the other side of the hairpin, usually assumed to be non-active.

Figure 7: A model of functional network with interactions among driver gene products and microRNAs regulating critical cellular processes leading to fibrotic reaction at ET lesions. It is being conjectured that cyclic bleeding associated with inflammatory and oxidative stress followed by repeated tissue injury and repair along with recurrent estrogenic stimulation and ovulatory events in the pelvic environment bring about the complex phenotype of atypical endometriosis with neoplasm with a trade-off malignant transformation in high risk women population.

Figure 8: Algorithm for pre-emptive monitoring and management of endometriosis-associated cancers (EACs). Although the prevalence of EACs is not alarmingly high, the cases of endometriosis depending on clinical details and patient's history may

be considered as pre-malignant field defect keeping Knudson's two-hit theory in perspective [232,233]. There is a need of deep histological examination to check for any evidence of atypia which should be followed by monitoring, management and treatment route so that malignant potential in high risk patients may potentially be avoided. It is evident that preservation of additional and serial tissue samples with detailed annotation is a strict requirement.

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