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## Endometrial Intraepithelial Neoplasia

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### 1. Introduction

Endometrial cancers are the most common malignancies of the female genital tract in the United States, with 42,160 new cases diagnosed and 7780 cancer-associated deaths in 2009 (Jemal, Siegel et al. 2009). The histopathological classifications of endometrial cancers are numerous, but in 1983, two broad clinico-pathologic categories of endometrial carcinomas were delineated (Bokhman 1983). This conceptual classification has largely been based on light microscopic appearance, clinical behavior and epidemiology, and had been subsequently supported by molecular-cytogenetic data, which has facilitated the acceptance of the so-called *dualistic model* of endometrial carcinogenesis (Deligdisch and Holinka 1987; Lax and Kurman 1997; Sherman 2000; Matias-Guiu, Catusus et al. 2001; Lax 2004; Liu 2007), a modified and more comprehensive comparison of both types is illustrated in Table 1.

According to that model, the first and the most common type of endometrial carcinoma is called *Type I endometrial cancer*. These Type I cancers, of which the pathologic prototype is endometrioid carcinoma, represent at least 80% of newly diagnosed cases of endometrial cancer. The much less common mucinous carcinomas are also generally classified as a Type I cancer. Overall, they occur in comparatively younger age group (40-50 years) (Deligdisch and Holinka 1987; Lax and Kurman 1997; Sherman 2000; Matias-Guiu, Catusus et al. 2001; Lax 2004; Liu 2007). The tumor cells frequently express estrogen and progesterone receptors (Demopoulos, Mesia et al. 1999; Lax 2004), and their evolution appears to be driven by unopposed estrogen stimulation from either endogenous (e.g. ovarian estrogen-producing tumors) and/or exogenous sources (e.g. hormonal therapy) (Ettinger, Golditch et al. 1988; Potischman, Hoover et al. 1996; Demopoulos, Mesia et al. 1999). These tumors, therefore, mostly arise in a background of endometrial glandular hyperplasia (Lax 2004; Liu 2007). *Type*

*I endometrial cancers* have a relatively favorable prognostic profile compared to *type II endometrial cancer* (Creasman, Odicino et al. 2003). Several kinds of genetic alterations had been detected in *Type 1 endometrial cancers*, including PTEN inactivation (Tashiro, Blazes et al. 1997; Mutter, Ince et al. 2001), beta-catenin (CTNNB1) mutations (Konopka, Janiec-Jankowska et al. 2007), and to a lesser degree, microsatellite instability (related to inactivation of the MLH1 gene) (Esteller, Levine et al. 1998), and activation mutations of the K-ras gene (Velasco, Bussaglia et al. 2006).

Parameters	Type I	Type II
Incidence	80%	15%
Peak Age	50-60	60-70
Obesity	Common	Uncommon
Estrogen stimuli	Common	Uncommon
Precancer	EIN (classic)	EmGD (serous type & clear cell type)
Latent Precancer	PTEN null glands	P53 signature glands
Progression	Slow	Rapid
Histology	Endometrioid, mucinous	Serous, Clear cell, and Carcinosarcoma
Genetic changes	PTEN, MSI	p53, BRCA, 1pDel
Familial	HNPCC	Unknown
Prognosis	Good	Poor

Table 1. Dualistic model of endometrial cancer as modified by Zheng et al (Zheng, Xiang et al. 2011).

*Type II endometrial cancer* in the dualistic model are significantly less common than their Type I counterparts, and represent only 10- 15% of cases. The pathologic prototype of this category is the endometrial serous carcinoma (ESC) [previously termed uterine papillary serous carcinoma (UPSC)]. *Type II endometrial cancer* typically occurs in an older age group (60-70 years) (Lax and Kurman 1997; Sherman 2000; Matias-Guiu, Catusus et al. 2001). They frequently arise in a background of inactive or resting endometrium (Lax and Kurman 1997; Sherman 2000; Matias-Guiu, Catusus et al. 2001), display a low frequency of expression of hormonal receptors, are not associated with the estrogen-associated clinical factors (such as obesity) and generally are not thought to be directly influenced by hormones (Sasano, Comerford et al. 1990; Lax, Pizer et al. 1998; Demopoulos, Mesia et al. 1999; Lax 2004; Shang 2006). Definitive risk factors for *type II endometrial cancer* are still unclear, however. In one recent study, we found that women 55 years of age or under with a personal history of breast cancer, had an increased risk of ESC as compared with controls (Liang, Pearl et al. 2010), and an earlier study by Chan et al came to comparable conclusions 2006 (Chan, Manuel et al. 2006). These Type II cancers, most notably ESC, also exhibit frequent mutation and overexpression of the p53 (Sherman, Bur et al. 1995; Nordstrom, Strang et al. 1996) and HER2/neu (Rolitsky, Theil et al. 1999) genes and proteins, respectively. They also show alterations of intercellular adhesion molecules like E-cadherin (Holcomb, Delatorre et al.

2002; Mell, Meyer et al. 2004) and claudin (Santin, Bellone et al. 2007; Konecny, Agarwal et al. 2008), and display over-expression of p16 (Chiesa-Vottero, Malpica et al. 2007; Yemelyanova, Ji et al. 2009) and IMP-3 (Reid-Nicholson, Iyengar et al. 2006; Zheng, Yi et al. 2008). Overall, *type II endometrial cancer* have a relatively poor prognosis independent of other factors, and a higher mortality rate in comparison to type I cancers (Lauchlan 1981; Eifel, Ross et al. 1983; Sherman, Bitterman et al. 1992). This dualistic model has provided a valuable academic framework for the subsequent studies of myriad aspects of endometrial carcinogenesis and progression and a conceptual basis for the differential deployment of histotype-specific treatment modalities.

### 1.1 Endometrial Intraepithelial neoplastic lesions: The nomenclature dilemma

Endometrial cancers, especially *type II endometrial cancer*, are a significant cause of morbidity and mortality in women (Jemal, Siegel et al. 2009). This has prompted the long-standing search for optimal approaches for their prevention; one aspect of prevention is the early recognition of occult *precursor lesions* or *precancers* (Berman, Albores-Saavedra et al. 2006), along with the administration of therapeutic interventions prior to the development of overt malignancy. To establish any lesion as a precursor lesion or a precancer to one neoplasm, the putative lesion should meet some basic criteria that defines a precancer, as recognized by participants at a consensus conference on the subject sponsored by the National Cancer Institute in 2006 (Berman, Albores-Saavedra et al. 2006). This definition modifies and generalizes a definition initially proposed for endometrial intraepithelial neoplasia (Mutter 2000; Mutter, Baak et al. 2000; Mutter, Ince et al. 2001; Mutter 2002; Hecht and Mutter 2006; Mutter, Zaino et al. 2007). The following five defining criteria must all be met: “(1) Evidence exists that the precancer is associated with an increased risk of cancer. (2) When a precancer progresses to cancer, the resulting cancer arises from cells within the precancer. (3) A precancer is different from the normal tissue from which it arises. (4) A precancer is different from the cancer into which it develops, although it has some, but not all, of the molecular and phenotypic properties that characterize the cancer. (5) There is a method by which the precancer can be diagnosed”. In the last two decades, there have been significant advances made in the study of the precursors of *Type I endometrial cancer*, and this precancerous lesion is currently considered as endometrial atypical hyperplasia in the WHO classification system (that is still the most frequently used by pathologists) and the “endometrial intraepithelial neoplasia (EIN)” system that was originally proposed by Mutter et al (Mutter 2000; Mutter, Baak et al. 2000; Mutter, Ince et al. 2001; Mutter 2002; Hecht and Mutter 2006; Mutter, Zaino et al. 2007). On the other hand, studies of *Type II endometrial cancer* precursors have been relatively limited. The prototype of *Type II endometrial cancer*, which is ESC, usually arises in a background of atrophic or resting endometrium. This is in contrast to *Type I endometrial cancer*, which generally have a hyperplastic (or at least non-atrophic) background and show a strong relation to high estrogen levels. For this and a variety of other reasons, the precancers of *type I endometrial cancer* are highly unlikely to constitute the precancer lesions for *Type II endometrial cancer*. Numerous lines of evidence developed during the last decade point toward a newly recognized lesion called “endometrial glandular dysplasia (EmGD)” as the actual precursor of Type II cancers, including serous and clear cell types (Zheng, Liang et al. 2004). These lines of evidence include pathologic, genetic as well as clinical factors. Accordingly, the precancer of *type I endometrial cancer* and *type II endometrial cancer* are two distinct entities at the morphologic and molecular

levels and are not related to each other. In this chapter, we explore the current state of knowledge on all types of precancerous lesions of the endometrium, based on our interpretation and modification of the dualistic model of endometrial carcinogenesis. Clinical and pathological experience in endometrial carcinogenesis had shown a significant impact of histologic subtype (endometrioid, serous, clear cell etc) on overall prognosis and survival. Considering the multiple conflicting nomenclatures that existed in studies of endometrial carcinogenesis, which lead to the inappropriate inclusion of some entities as 'precancers' (as discussed in following sections), we plan to propose a unified terminology and classification scheme for the precancerous lesions in the endometrium, which will be biology-based and clinically oriented for better patient care. Accordingly, the discussion of intraepithelial neoplastic lesions of the endometrium would embrace the precancer of *type I endometrial cancer*, which we will refer to as endometrioid EIN; as well as the precancers of *type II endometrial cancer*, that is, serous EmGD and clear cell EmGD, which will be referred to as serous EIN and clear cell EIN respectively. As summarized in Figure 1.

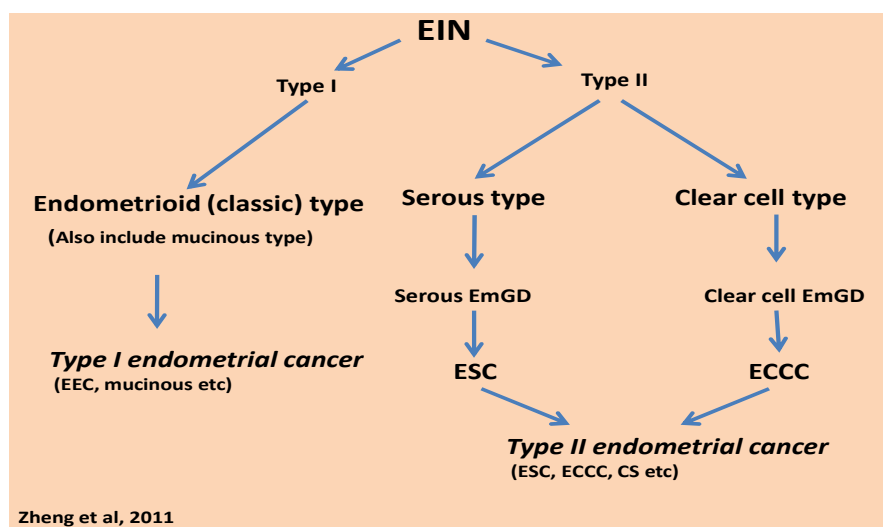


Fig. 1. A proposed unified model of endometrial carcinogenesis. Endometrial intraepithelial neoplasia (EIN) encompass a broad spectrum of morphologically and biologically distinct entities, categorized as type I, referring to the classic EIN lesion described by Mutter, and type II that include serous EmGD and clear cell EmGD as precancers of type II endometrial cancer.

## 2. Precancers of type I endometrial cancers

### 2.1 Historical backgrounds

In the past, *Type I endometrial cancer* was thought to be preceded by pan-endometrial hormonally induced changes referred to as endometrial hyperplasia. The term endometrial hyperplasia encompasses a broad spectrum of polyclonal proliferations that result from a physiological response of the endometrium to an abnormal estrogenic stimulus. The magnitude of such proliferations, reflects the quantity and duration of unopposed estrogen exposure (Trial 1996; Mutter, Zaino et al. 2007), resulting in architecturally variable glands covering a surface area that is equal or exceeds that of the stroma (i.e. gland-stroma ratio more than 1:1). The most widely observed histological features include irregular architectural remodeling of endometrial glands in functionalis layer, vascular thrombi, and

stromal breakdown. A critical feature of benign hyperplasia is that no significant cytological changes are seen between the hyperplastic glands and the surrounding glands (Mutter, Zaino et al. 2007). Benign endometrial hyperplasia is most frequent around the time of the menopause, due to alterations of the normal cycle of sequentially regulated estrogen and progesterone. It may also occur following anovulatory cycles for the same reason. The most common symptoms of hyperplasia are prolonged or excessive bleeding at intervals that are initially longer than normal. Microinfarcts and estrogen withdrawal are responsible for symptomatic bleeding (Song, Rutherford et al. 2002; Ferenczy 2003). Other patients may complain of intermittent spotting, commonly attributed to patchy stromal breakdown secondary to estrogen-induced microthrombi. A rapid decline in the prolonged estrogen stimulation causes massive apoptosis of the endometrial glands and stroma resulting in heavy shedding. Occasionally, the decrease in estrogen levels is sufficiently gradual that generalized apoptosis and shedding fail to take place as regular menstruation.

The World Health Organization (WHO) 1994 classification system subdivided endometrial hyperplasia according to architectural complexity and cytological atypia into 4 subgroups: simple, simple hyperplasia without atypia, complex, and atypical complex hyperplasia (Scully RE 1994), as illustrated in Figure 2. The WHO 1994 endometrial hyperplasia schema confines most precancers of *type I endometrial cancer* in the atypical hyperplasia subgroup, but in the opinion of many pathologists and investigators, there are several problems associated with this classification. First, this classification system is poorly reproducible among pathologists (Hunter, Tritz et al. 1994; Skov, Broholm et al. 1997; Zaino 2000). Second, this system is missing diagnostic elements that have only become clear in recent years. Of these elements, the localizing topographic distribution of a clonally expanding precancer and the need to establish size thresholds for diagnosis. Third, it is a purely morphology-based system without any supporting molecular and morphometric studies that precisely quantifies diagnostic architectural changes. The search for an alternative classification system for endometrial carcinomas had led to the introduction of the Endometrial Intraepithelial Neoplasia (EIN) entity.

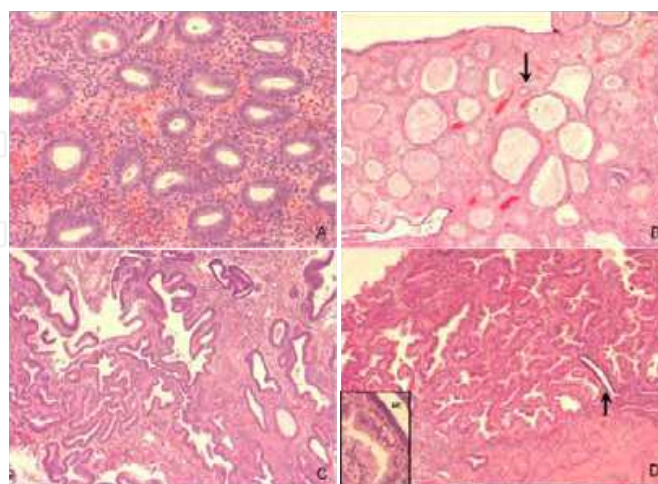


Fig. 2. A: simple hyperplasia, B: simple hyperplasia without atypia, C: complex hyperplasia, D: atypical complex hyperplasia. Arrows indicate residual uninvolved glands. Inset: magnified area with arrow, a hyperplastic gland shows atypical distinct morphology compared to adjacent resting endometrial gland (RE).

## 2.2 EIN: Mutter's model for *type I endometrial cancer*

The concept of EIN and the diagnostic schema was introduced by Mutter and the Endometrial Collaborative Group in 2000 (Mutter 2000); and later launched at Brigham and Women's Hospital in 2002 (Mutter 2002; Hecht, Ince et al. 2005), to replace the older hyperplasia-based nomenclature, the currently used terminology by WHO 1994 classification system (Scully RE 1994), which implies endometrial hyperplasia as the precancerous lesion of type I cancers. This concept was the result of cautious correlation of genetically ascertained pre-malignant lesions with histopathologic feature and clinical outcomes. A better vision of the carcinogenesis of *type I endometrial cancer* was achievable with the advent of polymerase chain reaction-based clonal assays and relevant biomarkers that facilitated a molecular, rather than purely morphologic approach to precancer diagnosis. The molecular entity of EIN is thought to be a clinically pertinent lesion that can be reproducibly diagnosed by pathologists and targeted for therapeutic intervention. According to this model, the premalignant lesions are referred to as EIN to distinguish them from the diffuse estrogen associated changes of benign endometrial hyperplasia. EIN is a "histologically recognizable localized lesion composed of a clonal proliferation of glands and that usually carry one or several of the genetic abnormalities associated with endometrioid carcinoma" (Mutter, Boynton et al. 1996; Mutter, Baak et al. 2000). This model had been supported by molecular and morphometric studies. First, the monoclonality of EIN lesions was proven utilizing nonrandom X-chromosome inactivation (HUMARA assay) and clonal propagation of altered microsatellites (Mutter, Chaponot et al. 1995; Jovanovic, Boynton et al. 1996). Second, the identification of lineage continuity with subsequent carcinomas that occur in the same patient, fulfilling a vital standard for molecular definition of precancers (Mutter, Baak et al. 2000). Third, the application of computer based morphometry has been successful at further improving diagnostic reproducibility of precursor diagnosis, and have a better correlation between morphologic features and patient actual clinical outcome (Baak, Nauta et al. 1988; Baak, Wisse-Brekelmans et al. 1992). The applied morphometric measures were combined into a threshold D-score (detailed below). In 2005, a meta-analysis study of the cumulative outcome prediction experience of the D-score (Baak, Mutter et al. 2005), showed that patients with a D-score less than 1 have an overall 89-fold increased cancer risk than those with D-score more than 1. Even if one excludes concurrent cancers, those diagnosed within 12 months of EIN, cancer risk over the next two decades is 45-fold that of controls. Comparison of the WHO 94 and the EIN systems, with correlation of the clinical outcome reveals a degree of overlapping. Mutter et al (Hecht, Ince et al. 2005) had found that, for the simple non-atypical hyperplasia, only a minimal risk for endometrial cancer is believed to be present (only 5% are re-diagnosed as EIN upon review). Complex atypical hyperplasia has the highest risk of cancer and 80% of cases are re-diagnosed as EIN (the greatest overlap). Therefore, majority of EIN lesions are actually equivalent to most of the WHO atypical complex hyperplasia category. Detailed relationship is illustrated in Figure 3.

### 2.2.1 Diagnostic features of EIN

As defined by Mutter et al, EIN is 'the premalignant clone of an endometrial lesion that is characteristically offset from the background endometrium by its altered cytology and crowded architecture'. This definition implies the use of an internal control for cytologic atypia, which is the benign resting endometrium, combined with the distinctive topography of a clonal process. The average age of women with EIN is 52 years (Baak, Mutter et al.

2005), almost a decade younger than the average age for cases of endometrioid endometrial carcinoma in patients with concurrent endometrioid carcinoma (Baak, Mutter et al. 2005; Hecht and Mutter 2006), and when those patients are excluded, the average time following EIN detection to carcinoma diagnosis is 4 years (Baak, Mutter et al. 2005). The clinical significance of EIN lesions is that they represent a long-term cancer risk that is 45-fold greater than that of their benign endometrial hyperplasia counterparts (Hecht and Mutter 2006; Mutter, Zaino et al. 2007). This distinctive clinical profile, is further supported by morphometric measures, summed up under the term D-score, which includes the volume percent stroma (a measure of gland crowding); standard deviation of the shortest nuclear axis (a measure of nuclear pleomorphism); and gland outer surface density (a measure of branching and folding). The morphometric techniques were effective at discriminating those endometrial lesions which progress to adenocarcinoma from those that do not (Baak, Nauta et al. 1988). However, we would like to point out that the morphometric techniques are so far mainly limited to research applications rather than in general practice.

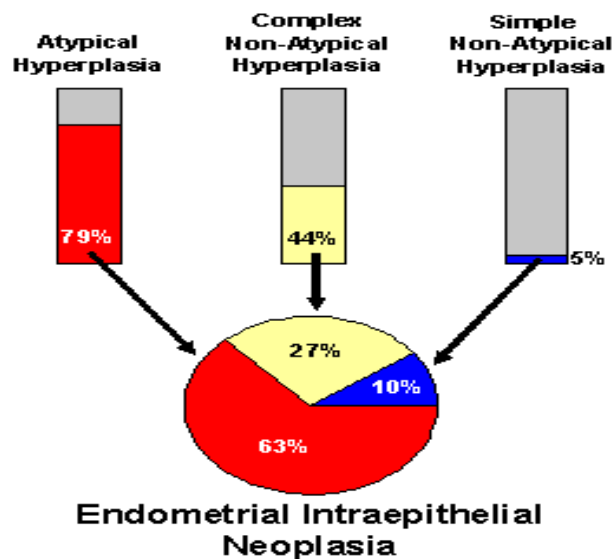


Fig. 3. Mutter's diagram (Hecht, Ince et al. 2005) for overlaps between WHO and EIN classification systems.

Based on the model of EIN, 5 strict morphologic features are applied, and all 5 criteria must be met in each case to maintain a high level of diagnostic specificity and predictive value. The diagnostic criteria are summarized in Table 2.

### Architecture

A feature that makes EIN lesions readily visible under low magnification. Area of glands exceeds that of stroma, thus, the surface area of glands (combined epithelium and lumen) is greater than that of the stroma that contains them, and the tissue proportion occupied by stroma is less than 50%. However, this ratio is also used as a diagnostic feature for benign endometrial hyperplasias. To overcome the potential source of diagnostic confusion, strict search for the other 4 criteria is critical to confirm the lesion in question is EIN and not a focus of endometrial hyperplasia. Another important point to mention is the condition of the endometrial stroma within the area of question.



EIN feature	Definitions
<b>Architecture</b>	Area of glands exceeds that of stroma (glands/stroma > 1). Lesion composed of individual glands, which may branch slightly and vary in shape.
<b>Cytology</b>	Nuclear and/or cytoplasmic features of epithelial cells differ between glands with abnormal architecture and those with normal background. May include change in nuclear polarity, nuclear pleomorphism, or altered cytoplasmic differentiation state. Highly abnormal cytology if no normal comparison glands are present
<b>Size</b>	Maximum linear dimension exceeds 1 mm
<b>Exclude benign mimics</b>	Benign conditions with overlapping criteria :disordered proliferative, basaloid, secretory, polyps, repair, etc.
<b>Exclude cancer</b>	Carcinoma if mazelike glands, solid areas, or significant cribriform growth.

Table 2. Essential diagnostic criteria of EIN as outlined by Mutter et al (Mutter, Zaino et al. 2007).

### Cytologic Changes

This must be judged individually in each case using the native background endometrium as the internal control (Figure 4 A). No unified diagnostic cytologic features are settled for EIN, this is due to several factors. First, the variability of the cytological characteristics of the endometrial glandular epithelium among specimens, according to fixation, processing, and staining. Second, this inconsistency also depends largely on the fluctuating hormonal environment. Third, not all EIN lesions maintain endometrioid differentiation (Mutter, Zaino et al. 2007), and commonly acquire metaplastic changes, including mucinous,

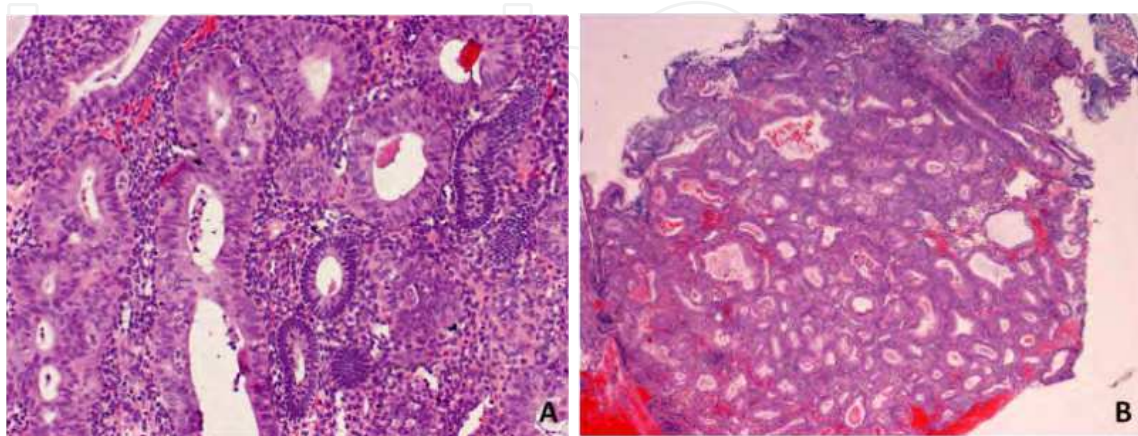


Fig. 4. Diagnostic features to look for in EIN lesions. EIN glands are cytologically distinct from the surrounding normal endometrial glands (A, 200x). The lesion should be at least 1mm in dimension (B, 40x).

squamous morular, tubal, eosinophilic, or micropapillary changes. The practicing pathologist should be careful, however, not to confuse the relatively mild cytologic atypia of EIN lesions with the striking atypia with possibly hobnailed nuclei seen in the precancer of *type II endometrial cancer* (serous EmGD and clear cell EmGD).

### Size

The lesion must be at least 1 mm in dimension in a single tissue fragment (Figure 4B). This “golden” number needs to be present in only one dimension of the lesion. Separate foci cannot be added to achieve this minimum size, it must be met in a single focus (Mutter, Zaino et al. 2007). The reason why a size parameter is needed in such a lesion, is probably to confer reproducibility and predictive value in pathological and the clinical sides, respectively. It may also significantly reduce the risk of EIN overdiagnosis in minute randomly detected foci of glandular crowding. One problem of the size limit is that about 20% of EIN lesions are diffuse and non-localized by the time they are detected (Mutter, Zaino et al. 2007), such a diagnostic difficulty might be overcome by largely depending on the other diagnostic criteria. Lesions that have most of the diagnostic criteria for EIN but are <1mm in dimension are still of unknown clinical significance, but are thought to be a good indication for subsequent follow-up endometrial sampling. However, in a recent study by Huang et al (Huang, Mutter et al. 2010), 71 579 consecutive gynecological pathology reports were retrieved, of which, 206 (0.3%) cases with ‘gland crowding’ were identified, in which 69% (143/206) had follow-up sampling. Of these, 33 (23%) had an outcome diagnosis of EIN (27 cases; 19%) or carcinoma (6 cases; 4%). Included were 18 cases (55%) diagnosed within the first year and presumed concurrent, and an additional 15 (45%) discovered after 1 year and interpreted as a later phase of disease or new events (Huang, Mutter et al. 2010). The authors suggested that such “gland crowding” is significant and deserves mention in pathologic reports.

### Exclusion of benign mimics

Many innocent conditions are frequently encountered during routine examination of endometrial specimens, and these may be the source of diagnostic difficulty in the exclusion of a potential EIN lesion. These may include (but are not limited to) artifactually pushed together or telescoped endometrial glands; or crowding related to the late secretory endometrium, in which the gland density may be very high in the deep functionalis where predecidual change is minimal (Figure 5A). Some portions of specialized but otherwise normal endometrium such as lower uterine segment or uterine basalis may also cause confusion, these are usually identified by their fibrous stromal context and quiescent epithelium. Another more serious misinterpretation comes when dealing with endometria under the influence of estrogen withdrawal, either during the normal menstruation or as a result of hormonal imbalances, the resulting microscopic picture is collapsed glands and stromal condensation. This frequently results in irregular glands lacking much stromal separation, giving an EIN-like picture (Figure 5B). Overall, the most commonly overdiagnosed lesions as EIN are probably endometrial polyps (as well as with endometrial hyperplasia), yet, their characteristic altered stroma and thick vessels, are readily distinct from the stromal features of EIN.

### Exclusion of cancer

EIN lesions are composed of clusters of individually recognizable glands, whereas endometroid carcinoma show more complex growth patterns not seen in EIN, such as solid,

cribriform, or complex interlacing mazelike growth (Figure 6A &B). The presence of myoinvasion is also diagnostic of carcinoma (Figure 6C), but this is better applied to hysterectomy specimens where intact myometrial wall is present. Overly malignant cytologic features beyond that seen in EIN are also present (Figure 4D).

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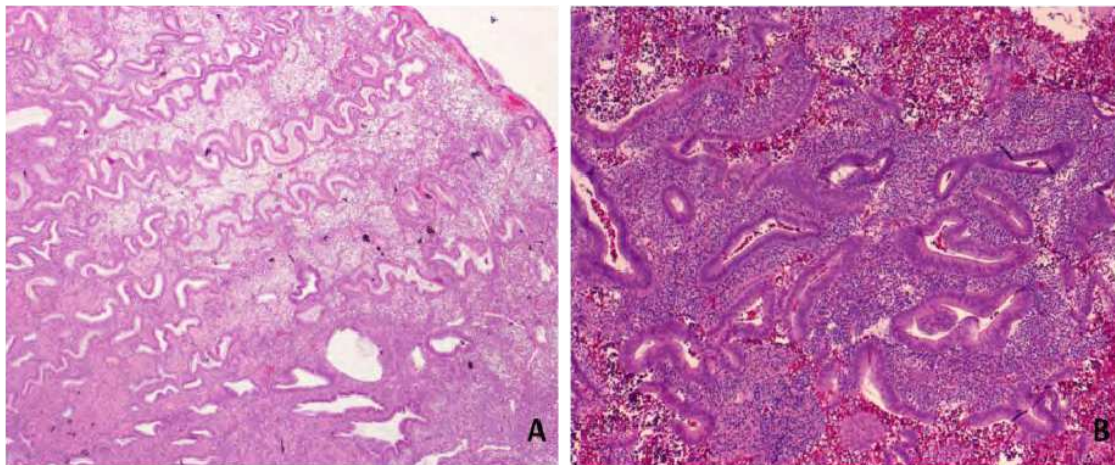


Fig. 5. Benign mimics of EIN. Late secretory endometrium displays prominent tortuous glands and crowding (A, 40x). Breakdown changes with artificially crowded irregular glands due to stromal collapse (B, 100x).

In our current proposal for a unified and simplified nomenclature for the precancers of endometrial cancers, we prefer to refer to this classic EIN entity described above as 'endometrioid EIN'.

### 2.2.2 Differential diagnosis

Many of the important mimics of EIN lesions have been discussed in the preceding sections (exclusion of benign mimics and exclusion of cancer). Another differential diagnostic consideration that is worth mention is the precancer of *type II endometrial cancer* (in our opinion, serous EmGD and clear cell EmGD). Unlike *type II endometrial precancers*, endometrioid EIN cells lack high-grade cytologic features, including hobnail nuclei. Also endometrioid EIN usually has a high-level estrogen stimulation, yet this is not the usual scenario in serous or clear cell EIN. Immunohistochemical studies with p53 and IMP3 are useful as these markers are positive in serous EmGD but not in endometrioid EIN.

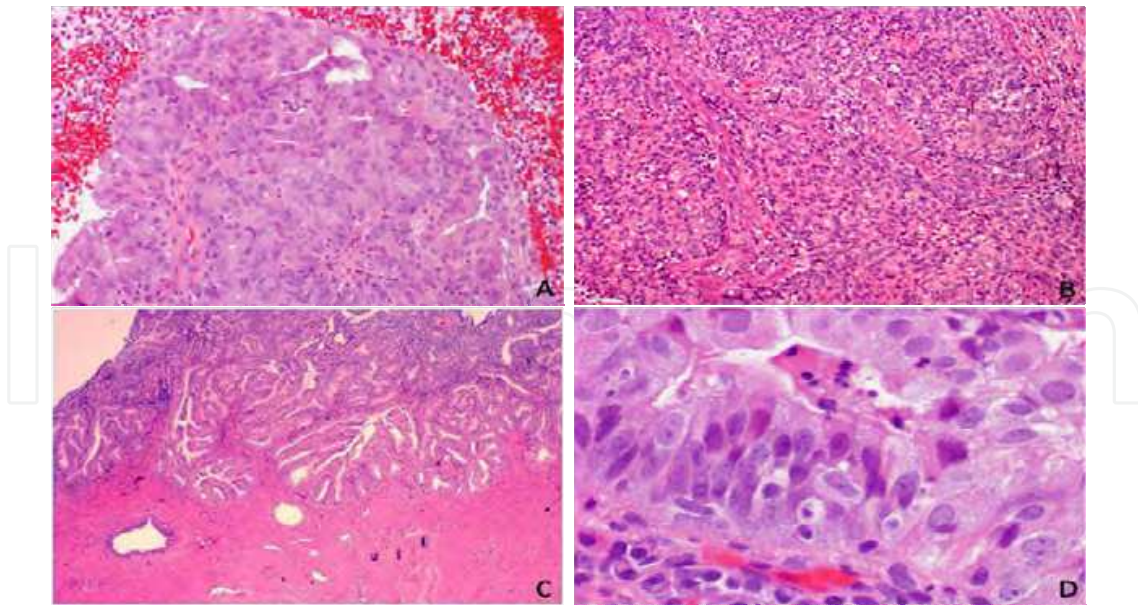


Fig. 6. Features of endometrioid carcinoma, and not EIN. Cribriform glands (A,100x), solid growth pattern (B, 40x), presence of muscular invasion (C, 20x), or frankly malignant cytologic features (D, 200x).

## 2.3 Molecular insights

### 2.3.1 *Type I endometrial cancer and sex hormones*

The normal endometrial epithelial cells are highly responsive to sex hormones, namely, estrogens and progesterone; and the morphology of the endometrium at any point is the sum of these responses and interactions. Consequently, the risk for *type I endometrial cancer* is significantly affected by the reciprocal and “opposing” actions of estrogens and progesterones, and is a dynamic process that depends on temporal changes in tissue responsiveness. The same is true for the resultant cancer in which the neoplastic cells retain this feature of hormone-responsiveness. Studies of the expression profiling of *type 1 endometrial cancer* cells had shown resemblance to the expression profile seen in estrogen-driven proliferative endometrium, it also lacks expression of some genes induced by progestins (Hecht and Mutter 2006).

On one hand, estrogens are promoters of cell proliferation and inhibitors of apoptosis, the effect of which is a manifestation of a complex downstream sequence of transcription changes that may involve modulation of tumor suppressor genes. These changes may include alterations in PTEN, PAX2, and HOXB13 among others. PTEN expression in normal endometrial glands is greatly elevated by estrogens and reduced by progestins during hormonal fluctuations of the normal menstrual cycle (Mutter, Lin et al. 2000). As promoters of proliferative activity, estrogens may also increase probability of arbitrary mutations (Cairns 1998), as well as increase the rate of mutagenesis through free radical formation (Burcham 1999), although the magnitude of this effect is minimal. Overall, large-scale population studies had shown that women exposed to “unopposed” estrogens have 2 to 10 folds increased risk for *type I endometrial cancer*, and this wide range is influenced by the dose and duration of exposure (Parazzini, La Vecchia et al. 1991; Potischman, Hoover et

al. 1996; Trial 1996; Zeleniuch-Jacquotte, Akhmedkhanov et al. 2001). Moreover, EIN lesions are thought to attain high levels of nuclear estrogen receptors (Mutter, Ince et al. 2001), thus, estrogens may also act as growth positive selectors of the previously mutated cells, allowing their clonal expansion.

On the other hand, progestins have the ability to “oppose” the biologic effects of coexisting estrogens through down-regulation of the estrogen receptor itself in the endometrial epithelial cells. This is actually the basis of combined estrogen/progesterone therapies, in which the net effect is dominated by the progestin component. It is also known to be the reason behind the protective influence of combined oral contraceptives, women who uses these drugs are said to have 0.5 to 0.7 fold risk of *type I endometrial cancer* compared to controls (Grimes and Economy 1995; Weiderpass, Adami et al. 1999). Other protective effects of circulating progestins are due to downregulation of proliferative promoters like PTEN, thus it was found that PTEN mutant clones have a tendency to involute under the influence of progestins (Zheng, Baker et al. 2004). The anti-cancer role of progestins is further mediated by induction of apoptosis through the increased expression of Bcl-2 and BAX (Vereide, Kaino et al. 2005).

### 2.3.2 Molecular alterations in *type I endometrial cancer* and endometrioid EIN

*Type I endometrial cancer* demonstrate large numbers of genetic changes in which the sequential order of mutation, and the final combination of defects differ considerably between individual examples (Hecht and Mutter 2006). Common genetic changes in endometrioid carcinoma include, but are not limited to, microsatellite instability (MSI) (Risinger, Berchuck et al. 1993; Duggan, Felix et al. 1994; Kobayashi, Matsushima et al. 1996; Mutter, Boynton et al. 1996; Catusus, Bussaglia et al. 2004), or specific mutation of *PTEN* (Risinger, Hayes et al. 1997; Tashiro, Blazes et al. 1997; Levine, Cargile et al. 1998; Maxwell, Risinger et al. 1998; Gurin, Federici et al. 1999; Mutter, Lin et al. 2000), *K-ras* (Enomoto, Inoue et al. 1991; Fujimoto, Shimizu et al. 1993; Duggan, Felix et al. 1994; Sakamoto, Murase et al. 1998; Mutter, Wada et al. 1999; Swisher, Peiffer-Schneider et al. 1999; Lax, Kendall et al. 2000; Lagarda, Catusus et al. 2001), and  $\beta$ -catenin genes (Kobayashi, Matsushima et al. 1996; Fukuchi, Sakamoto et al. 1998; Mirabelli-Primdahl, Gryfe et al. 1999; Schlosshauer, Pirog et al. 2000). As previously described, it is the clonal origin of EIN that supports its definition as a precancer. Moreover, studies by Mutter et al gave considerable evidence that comparison of the type and magnitude of genomic damage between endometrioid EIN and *type I endometrial cancer* (Mutter, Boynton et al. 1996; Esteller, Catusus et al. 1999; Mutter, Baak et al. 2000; Mutter, Lin et al. 2000), indicates a greater cumulative mutational burden in the later, a feature considered one milestone in the definition of precancer (Berman, Albores-Saavedra et al. 2006). Below is a discussion of the most commonly encountered molecular alterations.

#### PTEN

Inactivation of the *PTEN* tumor-suppressor gene (formerly known as *MMAC1*) is the most common genetic defect in endometrioid carcinoma and is seen in up to 83% of tumors that are preceded by a histologically discrete premalignant phase (Mutter, Lin et al. 2000). It acts as tumor suppressor genes because their proteins may counteract the effect of the proteins encoded by the protein kinase group of protooncogenes (Matias-Guiu, Catusus et al. 2001).

The most frequently encountered alterations of PTEN in endometrial cancers are LOH at chromosome 10q23 (40% of EC) (Jones, Koi et al. 1994; Peiffer, Herzog et al. 1995); and somatic mutation, which are almost exclusively found in *type I endometrial cancer* (37 to 61%) (Kong, Suzuki et al. 1997; Tashiro, Blazes et al. 1997; Maxwell, Risinger et al. 1998; Bussaglia, del Rio et al. 2000). A number of investigators have found a concordance between microsatellite instability status and PTEN mutations; the mutations occur in 60% to 86% of MSI (+) endometrioid carcinoma, but in only 24% to 35% of the MSI (-) tumors (Matias-Guiu, Catusus et al. 2001). Such results have led to the assumption that PTEN could be a likely target for mutations in MSI (+) EC. PTEN inactivation was detected frequently in EIN lesions (63% of cases) (Mutter, Ince et al. 2001). However, the routine application of PTEN as an informative marker of premalignant lesions is still questionable due to several facts. First, PTEN mutations have been detected in endometrial hyperplasia with and without atypia (19% and 21% respectively) (Levine, Cargile et al. 1998; Maxwell, Risinger et al. 1998; Bussaglia, del Rio et al. 2000). Second, the lack of PTEN inactivation in about one third of studied EIN lesions (Mutter, Zaino et al. 2007). And finally, the finding of somatic inactivation of PTEN in scattered benign endometrial gland in 43% of cases. (Mutter, Ince et al. 2001)

### **B-catenin (CTNNB1)**

Gain of function mutations in exon 3 of *CTNNB1* gene at 3p21 are seen in 25% to 38% of *type I endometrial cancers* (Fukuchi, Sakamoto et al. 1998; Schlosshauer, Pirog et al. 2000). B-catenin is a component of the E-cadherin-catenin unit essential for cell differentiation and maintenance of normal tissue architecture, and plays an important role in signal transduction (Hecht and Mutter 2006). B-catenin mutation may represent a pathway to endometrial carcinogenesis characterized by squamous differentiation and independent of PTEN (Su, Vogelstein et al. 1993). B-catenin expression change is usually a diffuse process seen in all tumor cells, and is present in some premalignant lesions (Hecht and Mutter 2006). This suggests that B-catenin mutation is an early step of endometrial tumorigenesis that is clonally represented in all tumor cells (Matias-Guiu, Catusus et al. 2001; Saegusa, Hashimura et al. 2001; Hecht and Mutter 2006). Furthermore, B-catenin might regulate the expression of the matrix metalloprotease-7, which would have a role in the establishment of the microenvironment necessary for the initiation and maintenance of growth of the primary tumors and their metastasis. (Brabletz, Jung et al. 1999). Further studies are needed to explore the role of B-catenin in *type I endometrial cancer* carcinogenesis.

### **K-RAS**

*K-RAS* mutations have been identified in 10% to 30% of *type I endometrial cancer* (Sasaki, Nishii et al. 1993; Swisher, Peiffer-Schneider et al. 1999; Lax, Kendall et al. 2000). There is a higher frequency of *K-ras* mutations in cancers with microsatellite instability (MSI), and many of these are characterized by methylation related GC3AT transitions (Lagarda, Catusus et al. 2001). Several investigators had previously found associations between k-RAS mutations and the presence of coexistent endometrial hyperplasia, (Tsuda, Jiko et al. 1995) lymph node metastases, and clinical outcome in postmenopausal patients over 60 years of age (Ito, Watanabe et al. 1996). In addition, some investigators have reported an almost complete absence of k-RAS mutations in serous and clear cell carcinomas of the endometrium (Caduff, Johnston et al. 1995). In the study by Mutter et al (Lagarda, Catusus

et al. 2001), the authors reported k-RAS mutations in 18.9% of 58 endometrial cancers, all of them were of endometrioid type. They also described a higher frequency of k-RAS mutations in MSI (+) carcinomas (6 of 14, 42.8%) than in MSI (-) tumors (5 of 44, 11.3%), which lead to the assumption that k-RAS mutations are common in endometrial cancer with the microsatellite mutator phenotype. In the same series, k-RAS mutations were detected in only one of 22 endometrial hyperplasia cases. In this case, atypical hyperplasia coexisted with carcinoma; interestingly, both lesions exhibited MLH-1 promoter hypermethylation, MSI, and identical PTEN mutations, but they had different k-RAS mutations; of the remaining 21 endometrial hyperplasias, 6 had shown MLH-1 promoter hypermethylation and one had both MLH-1 methylation and MSI. Accordingly, the authors hypothesized that “both k-RAS and MSI are closely related phenomena that may occur simultaneously before and during clonal expansion”.

### Microsatellite instability (MSI)

Among sporadic *type I endometrial cancer* of all grades, approximately 20% demonstrate a molecular phenotype referred to as Microsatellite instability (MSI) (Risinger, Berchuck et al. 1993; Burks, Kessis et al. 1994; Duggan, Felix et al. 1994; Mutter, Boynton et al. 1996). MSI is rare (< 5%) in *type II endometrial cancer* (Faquin, Fitzgerald et al. 2000; Goodfellow, Buttin et al. 2003). Microsatellites are short segments of repetitive DNA bases that are scattered throughout the genome; they are found predominantly in noncoding DNA. Due to DNA repair errors made during replication, the tendency to develop changes in the number of repeat elements as compared with normal tissue is termed MSI. MLH1 inactivation, a component of the mismatch repair system, is the most common mechanism in endometrial carcinoma and is accomplished by hypermethylation of CpG islands in the gene promoter, a process known as epigenetic silencing. (Esteller, Levine et al. 1998) Inherited or somatically acquired mutations of *MSH6*, another mismatch repair element, are also common in patients with MSI endometrial cancers. (Goodfellow, Buttin et al. 2003) MSI in general, and abnormal methylation of MLH1 in particular, is an early event in endometrial carcinogenesis that has been described in precancerous lesions (Mutter, Boynton et al. 1996; Levine, Cargile et al. 1998; Esteller, Catusus et al. 1999). The significance of MSI may also be a result of its ability to specifically inactivate other genes which contain susceptible repeat elements, such as transforming growth factor receptor type II, (TGF- $\beta$ RII), BAX, insulin-like growth factor II receptor (IGFIIR), and hMSH3, resulting in secondary tumor sub-clones with an increased capacity to invade and metastasize (Ouyang, Shiwaku et al. 1997; Catusus, Matias-Guiu et al. 2000).

### p53

p53 is a nuclear phosphoprotein that provoke cell cycle arrest or apoptosis through induction of P21Waf1/Cip1 and hMdm2 in response to cellular stress (Hecht and Mutter 2006). Mutations involving p53 are among the most commonly encountered molecular abnormalities in *type II endometrial cancer* (detailed in subsequent sections), and are usually due to p53 truncation mutations (Alkushi, Lim et al. 2004). On the other hand, only 5% of *type I endometrial cancers* show aberrant accumulation of inactivated p53 protein (Lax, Kendall et al. 2000), may be secondary to changes in its upstream regulatory proteins (Soslow, Shen et al. 1998) rather than truncation mutations. Examples of such upstream regulatory molecules include *MDM2* and *p14 ARF*, that regulate p53 levels and their dysregulation had been shown to cause detectable levels of p53 in the absence of p53

mutation, and may be associated with adverse clinical outcomes (Soslow, Shen et al. 1998; Schmitz, Hendricks et al. 2000; Pijnenborg, van de Broek et al. 2006). p53 overexpression and high protein levels are thought to be associated with high grade and stage, but is also an independent prognostic factor (Alkushi, Lim et al. 2004). Other possible causes for p53 accumulation in *type I endometrial cancers* may be nonspecific DNA damage such as that induced by irradiation which is known to induce accumulation of wild-type p53 (MacCallum and Hupp 1999).

### 3. Precancers of type II endometrial cancer

#### 3.1 Precursor of endometrial serous carcinoma

##### 3.1.1 Historical backgrounds

Endometrial carcinoma with papillary features and psammoma bodies had been described in the literature as early as 1960s (Karpas and Bridge 1963; Hameed and Morgan 1972; Factor 1974). Nevertheless, the concept of “serous” differentiation and the distinguished aggressive behavior of such cancers were recognized 2 decades later by Lauchlan in 1981 (Lauchlan 1981), and shortly followed by Kempson and Hendrickson (Hendrickson, Ross et al. 1982). These concepts were further established by subsequent studies and case series focusing on morphologic features and patient survival relative to *type I endometrial cancer* (Lauchlan 1981; Eifel, Ross et al. 1983; Sherman, Bitterman et al. 1992). In 1992, Sherman et al illustrated 32 cases of endometrial cancer with a serous component (13 pure and 19 mixed histotypes), the author noted the presence of “cytologically malignant cells closely resembling the invasive serous carcinoma in the surface endometrium adjacent to the tumor” in 28 out of the 32 studied cases, and were entitled “intraepithelial carcinoma” (Sherman, Bitterman et al. 1992). Spiegel et al described a similar lesion in 1995, and designated it as “endometrial carcinoma in-situ” (Spiegel 1995). Within the same year, Ambros et al introduced the designation of endometrial intraepithelial carcinoma (EIC), as a lesion that was repeatedly and distinctively associated with endometrial carcinoma with a serous differentiation (Ambros, Sherman et al. 1995). Main histologic patterns illustrated in Figure 7.

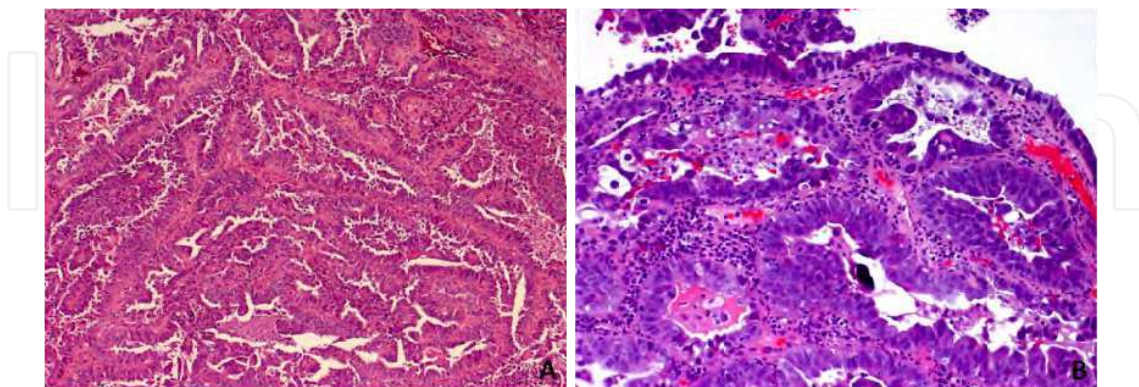


Fig. 7. Morphology of endometrial serous carcinoma. Papillary pattern (A) and glandular pattern (B).

However, in 1998, Zheng et al used the designation “uterine surface carcinoma” instead to describe that lesion, with emphasis on the multicentricity and relatively worse behavior in comparison to carcinoma in-situ per se, questioning the appropriateness of such a lesion as a



precancer (Zheng, Khurana et al. 1998). A similar approach had been published in 2000 by Wheeler et al, who proposed the term “minimal uterine serous carcinoma”, adding the size parameter (<1cm) to the definition of that lesion (Wheeler, Bell et al. 2000).

### 3.1.2 Zheng’s model for precursors of type II endometrial cancer

Serous EIC is still used in the most recent (2003)WHO classification as the precancerous lesion for serous endometrial carcinoma (Tavassoli FA 2003). However, in our opinion, the fact that stage 1A non-myoinvasive serous carcinomas are known to display extrauterine disease in 17-67% of studied cases (Carcangiu, Tan et al. 1997; Gehrig, Groben et al. 2001; Zheng and Schwartz 2005), strongly argues against the designation of serous EIC as a true “precancer”. Many years of gynecological surgical experience and studies of patient outcome have show that many patients diagnosed with serous EIC and treated with simple hysterectomy without surgical staging, had recurrences or intra-abdominal carcinomatosis (Carcangiu, Tan et al. 1997; Gehrig, Groben et al. 2001; Chan, Loizzi et al. 2003; Zheng and Schwartz 2005). Consequently, serous EIC is better recognized as an endometrial serous carcinoma with an early, non-myoinvasive growth pattern (Zheng and Schwartz 2005).

Careful examination of the definition of a precancer established in the National Cancer Institute Consensus in 2006, resulted in the conclusion that EmGD fulfills most of the defined criteria as a precancer of *Type II endometrial cancer*. The diagnostic criteria of serous EmGD were established by Zheng et al in 2004 (Zheng, Liang et al. 2004). Using morphological as well as immunohistochemical features, the EmGD lesions display changes that bridge the gap between benign endometrium and frankly malignant epithelium of serous EIC ( Figure 8); the dysplastic epithelium of EmGD has cytologic features that are more atypical than resting endometrium but fall short of serous EIC (Figure 9), as discussed in Table 3.

#### Macroscopic features

Grossly, no visible lesions could be identified in the corresponding areas of EmGD (Zheng, Liang et al. 2004).

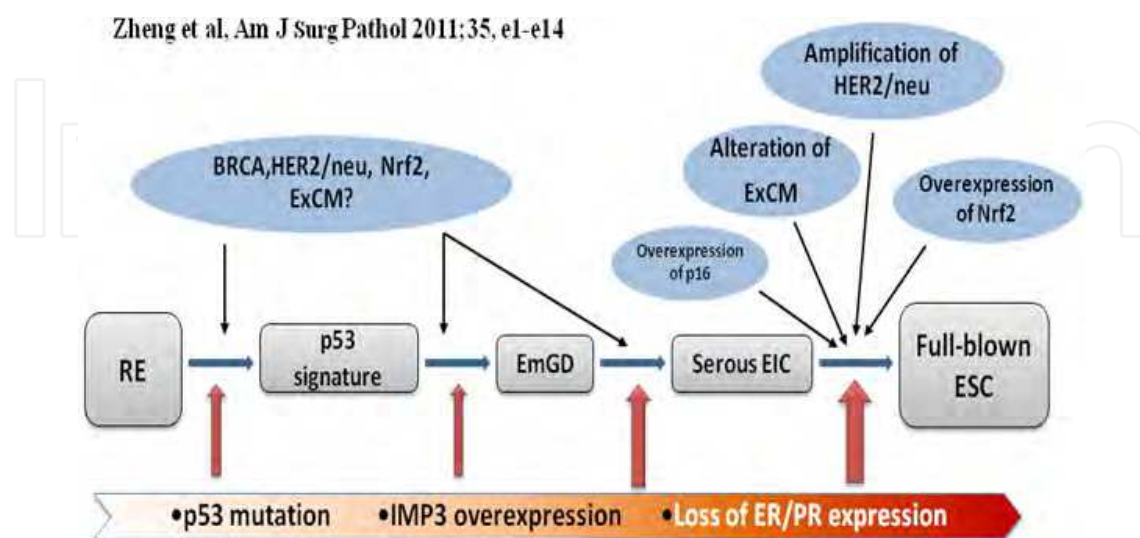


Fig. 8. Proposed model for endometrial serous carcinogenesis by Zheng et al (Zheng, Xiang et al. 2011).

### 3.1.3 Diagnostic criteria of serous EmGD

Serous EmGD Criterion	Comments
Patient age	Postmenopausal women, classically elder than 55 years old
Architecture & Cytology	Atypical endometrial glandular epithelium. The degree of atypia falls short of serous EIC. Many in endometrial polyp
Size limit and background	No size limit. Background is often atrophic or weakly proliferative, could be proliferative and rarely hyperplastic.
Exclude mimics	Benign conditions with overlapping features: bleeding or curettage associated atypia, repair, polyp with metaplastic changes
Exclude cancer	Serous EIC has frankly malignant cells same as in ESC/UPSC

Table 3. Serous EIN (serous EmGD) fact sheet

#### Microscopic features

The EmGD lesions are frequently multifocal (86% of cases) (Fadare and Zheng 2008). Classically, EmGD is characterized by glands and/or surface endometrial epithelium with atypical cytologic features. The cells of EmGD shows oval or round nuclei with a 2-3 folds nuclear enlargement compared with the benign resting endometrium. The nuclei are either hyperchromatic or with open chromatin patterns. When hyperchromasia is present, the degree of hyperchromasia is less than that of frankly malignant cells seen in serous EIC. Nucleoli are usually conspicuous instead of prominent. Partial loss of cell polarity is seen when nuclear stratification is present. A few stratifications may be seen. Mitotic figures and apoptotic bodies are appreciable, but not easily identified. Small papillary structures can be identified in EmGD glands, the thin fibrovascular cores of the EmGD papillae are also lined by dysplastic cells instead of malignant cells as in serous EIC or ESC. Occasional mitotic figures are present, but no abnormal mitoses are seen in EmGD lesions. Apoptotic bodies are scarce and in one of our series ranged from 0 to 5 per gland with an average of 1.5/gland (Zheng, Liang et al. 2004). The most common microscopic patterns include glandular involvement, either as a single or a group of EmGD glands within the endometrium or within an endometrial polyp. Another pattern is surface epithelial involvement of the endometrium or lining a polyp. EmGD foci are usually smaller than 1 mm in size. This may be related to the fact that they often presented as a single or a group of a few glands. However, occasionally, potential serous EmGD glands form clusters. When in endometrial polyps, the overall size of serous EmGD lesions may reach several millimeters. The stroma around the serous EmGD glands is usually fibrotic, but desmoplastic reactions are not seen. Background endometrium is often atrophic or weakly proliferative endometrium, but it could also be proliferative or rarely hyperplastic. This is actually a significant point to keep in mind, since nowadays; a considerable number of post-menopausal women are using hormonal replacement therapy compared to those who did 2 or 3 decades ago. In clinical practice, this is translated to the fact that about 40% of women with serous EIC or ESC have a non-atrophic endometrium as a background (Zheng, Liang et al. 2004) (34% proliferative,

6% hyperplastic endometrium). The significance of these findings is, in one hand, it provides further evidence that hormones are not risk factors for *type II endometrial cancer*; and on the other hand, pathologists should keep endometrial serous carcinoma as a differential diagnosis even in the existence of endometrial hyperplasia, in order to avoid the misdiagnosis of *type I endometrial cancer*, and the substantial consequences on patient management and outcome.

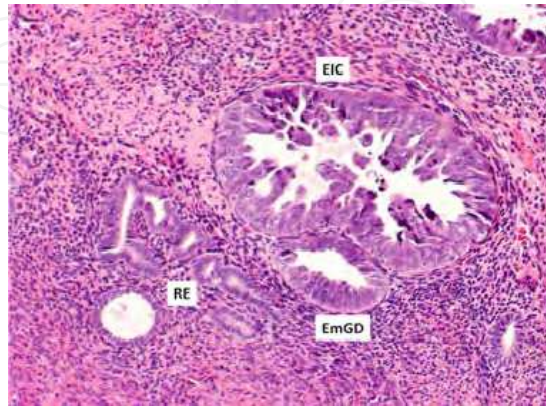


Fig. 9. Endometrial glandular dysplasia ( EmGD) morphology. EmGD bridges the morphologic gap between benign resting endometrium (RE) and endometrial intraepithelial carcinoma (EIC).

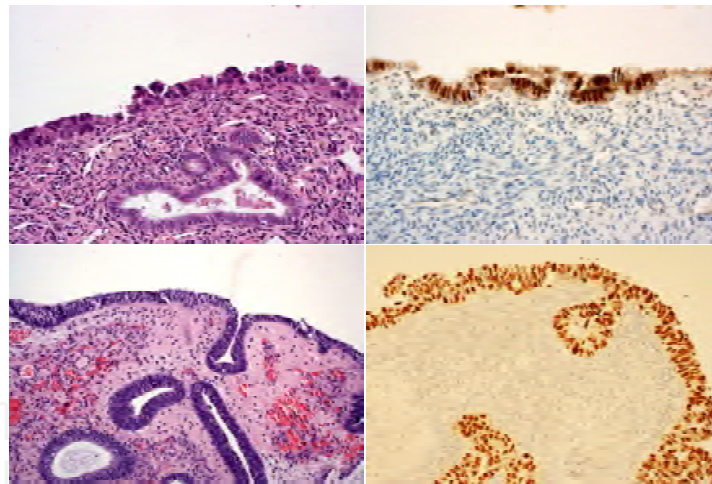


Fig. 10. p53 immunohistochemical stain in EmGD lesions. EmGD may involve the surface epithelium (upper left) or endometrial glands (lower left). The right panel shows diffuse nuclear positivity for p53 stain in areas corresponding to those in the left panel.

### 3.1.4 Molecular alterations of serous EIN

**p53 Mutations.** The p53 tumor suppressor gene, located on chromosome 17p 13.1, is probably the most commonly altered gene in human cancers (Harris 1993; Pietsch, Sykes et al. 2008), with the mutations commonly resulting in p53 protein over-expression (Darvishian, Hummer et al. 2004; Liang, Chambers et al. 2004; Jia, Liu et al. 2008). An extremely high rate of p53 alteration and over-expression (90% of our studied cases) had been detected in endometrial serous carcinoma, as evaluated by immunohistochemical

staining (Figure 10) (Zheng, Cao et al. 1996; Zheng, Khurana et al. 1998). In 2008, our group studied the frequency of TP53 gene mutations in exons 5 and 8 from laser-captured microdissected endometrial samples (Jia, Liu et al. 2008). In that specific context, the TP53 gene mutations had shown a successive increment from p53 signature glands (42%) to EmGD (43%), to serous EIC (63 to 72%), and to ESC (96%) (Jia, Liu et al. 2008). The benign endometria from the control group, in contrast, showed no mutation in non-signature glands. Analogous findings were found in a later study by Zhang et al in 2009 (Zhang, Liang et al. 2009). It is concluded that p53 gene mutation is a critical and early step in endometrial serous carcinogenesis, and that p53 is an important diagnostic immunohistochemical tool in this situation (Liang, Chambers et al. 2004; Jia, Liu et al. 2008; Zheng, Xiang et al. 2011).

### **BRCA Mutations**

A subset of relatively younger women with hereditary breast cancers are also at increased risk for the development of subsequent ovarian/tubal serous malignancies as a manifestation of hereditary breast-ovarian syndrome (Hall, Jamison et al. 2001; Arai, Utsunomiya et al. 2004), and in patients with BRCA mutations (Lavie, Hornreich et al. 2004). An earlier paper by Curtis et al in 1973, had described other malignancies that may follow breast cancer, including endometrial cancer (Inskip and Curtis 2007). The exact nature of this link between breast and endometrial cancer is still unclear; however, a few foundational studies had shed some light on evidences for such a relationship. In 1999, Hornreich et al reported a case of "uterine serous papillary carcinoma" in 2 siblings with both endometrial and ovarian serous carcinomas who were carrying identical mutation in BRCA1 gene (Hornreich, Beller et al. 1999). Genetic analysis showed loss of the wild-type allele, suggesting a link between germline BRCA1 mutation and serous cancer. A following study of Ashkenazi Jewish patients with endometrial serous carcinoma confirmed a high incidence of BRCA1 mutation and LOH (75% of tumor samples) (Lavie, Hornreich et al. 2004). A contradictory result was found in a study by the same group on a population of germline-BRCA mutation carriers, showing no relationship to increased risk of endometrial cancer. Another disagreement was reported by Liu et al, who found no significant increase in BRCA1 mutation in sporadic endometrial cancers (Liu, Ho et al. 1997).

Based on epidemiologic data, Chan et al had reported an association between breast cancer and endometrial cancers with aggressive histological types (Chan, Manuel et al. 2006). In 2007, a Swedish study found that 7.28% of patients undergoing genetic counseling for an increased risk of breast cancer, had family histories of both endometrial and breast cancers (von Wachenfeldt, Lindblom et al. 2007). We recently published a large cohort study that had found a history of a prior breast cancer in 20% of women with ESC, with the incidence being significantly higher in patients who were 55 years old or younger (41.5%) in comparison to those older than 55 years (16%) (Liang, Pearl et al. 2010).

In the light of the current controversy, further studies are absolutely needed to clarify the possible role of BRCA mutations in ESC. Contemporary data regarding BRCA mutations in serous EIC and EmGD lesions are still lacking.

### **Alteration of extracellular adhesion molecules**

Studies of the role of extracellular adhesion molecules in the development of ESC are limited relative to studies of tumor suppressor genes and oncogens. As aforementioned, ESC

has the unusual capacity to metastasize outside the uterus even in the absence of myometrial invasion. This might be linked to alterations of the extracellular adhesion molecules of the neoplastic serous epithelium. Such alterations likely assist the transtubal spread of ESC into the peritoneum, and consequently result in the advanced stage of disease at time of diagnosis, even with limited uterine disease. The phenomenon of transtubal spread of serous carcinoma cells had been emphasized by our study of serous EIC lesions in 2005 (Zheng and Schwartz 2005). In that study, 67% (6 out of 9) serous EIC cases had peritoneal carcinomatosis, and among these cases, 50% showed free-floating serous malignant cells and cell clusters in the tubal lumina (Zheng and Schwartz 2005). Our suggestion was further supported by the former findings of identical clones of cells in serous EIC and serous carcinomas at extrauterine sites (Kupryjanczyk, Thor et al. 1996; Baergen, Warren et al. 2001).

Of these extracellular molecules, *E-cadherin* and *claudins* had been described as potential contributors to the biological aggressiveness of ESC. E-cadherin downregulation had been previously reported to be associated with the progression of endometrial cancers (Sakuragi, Nishiya et al. 1994; Holcomb, Delatorre et al. 2002; Mell, Meyer et al. 2004). Holcomb et al described a reduction of E-cadherin expression in 62% and 87% of their studied serous carcinoma and clear cell carcinoma, respectively (Holcomb, Delatorre et al. 2002). A recent study showed that loss of E-cadherin may be attributed to L1CAM upregulation in the aggressive subtype of endometrial cancer (Huszar, Pfeifer et al.). Claudins are a family of extracellular tight junction proteins that are said to be up regulated in ovarian cancers (Rangel, Agarwal et al. 2003), and possibly related to cancer progression (Santin, Bellone et al. 2007). Expression of claudins, especially claudin-3 and claudin-4, is also higher in *type II endometrial cancers* relative to *type I endometrial cancers* (Konecny, Agarwal et al. 2008). *CD44* is a protein involved in cell adhesion and leukocyte homing, *CD44v6* is one of its isoforms that may be related to lymphovascular space invasion and metastasis. A significant loss of *CD44* and that particular isoform *CD44v6* had been detected in ESC compared to EEC (Soslow, Shen et al. 1998). *β-catenin* is a transcriptional activator downstream of the Wnt signaling pathway. Many types of human cancers harbor mutations of *β-catenin*, including endometrial cancers. Fukuchi et al (Fukuchi, Sakamoto et al. 1998) detected *β-catenin* mutations in 13% (10 out of 76) of their ESC cases. Whether or not serous EmGD show such alterations of extracellular adhesion molecules is still unclear and is the subject of future studies.

#### **Amplification of HER2/neu**

HER2/neu, also known as c-erb B2, is a protooncogene that encodes the human epidermal growth factor receptor (Gehrig, Groben et al. 2001). Amplification of HER2/neu and the overexpression of its protein had been shown in many human malignancies, including ESC (Santin, Bellone et al. 2002; Casalini, Iorio et al. 2004), some studies even described that in association with advanced stage and poor prognosis in ESC (Santin, Bellone et al. 2002; Vilella, Cohen et al. 2006). Although similar overexpression of HER2/neu by immunohistochemistry had been shown by the authors in serous EmGD and serous EIC in the studied cases, no data regarding the gene amplification is available so far.

#### **Overexpression of IMP-3**

Insulin-like growth factor m-RNA binding protein 3, or IMP-3 is a protooncogene expressed predominantly in embryonic tissues and rarely in adult tissues except for the placenta and

gonads (Nielsen, Christiansen et al. 1999; Yaniv and Yisraeli 2002). Some studies have revealed that IMP-3 is associated with cell migration and tumor invasion (Yaniv and Yisraeli 2002; Vikesaa, Hansen et al. 2006), and it could predict metastasis and prognosis in renal cell carcinoma (Jiang, Chu et al. 2006). In 2008, our group studied the expression of this oncofetal protein in serous endometrial carcinoma and its proposed precursor lesions using immunohistochemical staining (Zheng, Yi et al. 2008), we found that IMP-3 was overexpressed in 14% (3 of 21) EmGD lesions, 89% (16 of 18) serous EIC, and 94% (48 of 51) ESC cases. This was significantly higher than the expression detected in only 5 out of 70 (7%) EEC cases, and was not identified in its precancer lesion (EIN) (0 of 35 cases). These findings imply that IMP-3 overexpression may contribute in the early steps of ESC development and aggressive behavior (Zheng, Yi et al. 2008).

### **Overexpression of Nrf2**

NF-E2-related factor 2, or for simplicity, Nrf2, is a newly described transcription factor that is thought to boost the chemo-resistance of cancer cells (Wang, Sun et al. 2008). Nrf2 has been the subject of multiple studies by our group. In one of these studies in 2010 (Jiang, Chen et al.), Nrf2 showed high expression in 89% (41 of 46) of ESC cases, compared to marginal expression of Nrf2 in 28% (14 of 51) of EEC cases, while none of the studied benign endometria showed such an expression (0 of 20). Transient silencing of endogenous Nrf2 enhanced the sensitivity to chemotherapeutic agents in SPEC-2 cells derived from ESC (Zheng, Xiang et al. 2011). In addition, Overexpression of Keap1, a negative regulatory gene of Nrf2, significantly sensitized those ESC-derived SPEC-2 cells and its xenografts to chemotherapeutic drugs. More recently, we have also examined Nrf2 expression in precursor lesions of ESC, and found that Nrf2 was expressed in 40% of EmGD lesions, and 44% of serous EIC lesions in the studied cases (Chen, Yi et al.); it also showed a lesser degree of expression in clear cell carcinoma (13%) and its proposed precursor lesions, clear cell EmGD and EIC (10% and 25%), respectively. In the same study, only 6% of EEC (3 out of 50) and none of the atypical endometrial hyperplasia/EIN showed overexpression of Nrf2 (Chen, Yi et al.). The relationship between Nrf2 and early steps of ESC carcinogenesis and p53 mutations is currently under exploration in our laboratory.

### **Overexpression of p16**

p16, also known as CDKN2A, is a tumor suppressor gene that had been extensively studied in the context of HPV-related cancers and their precursors (Keating, Cviko et al. 2001; Keating, Ince et al. 2001; Negri, Egarter-Vigl et al. 2003). In cervical HPV-related cancers, the mechanism of p16 overexpression may be mediated by HPV E7 viral protein. More recently, p16 has been also shown to be overexpressed in the cells of ESC in multiple studies (Reid-Nicholson, Iyengar et al. 2006; Chiesa-Vottero, Malpica et al. 2007; Yemelyanova, Ji et al. 2009). The mechanism of this overexpression, however, is probably different from that described in viral-related malignancies, since HPV DNA in situ hybridization has been negative in all studied cases (Chiesa-Vottero, Malpica et al. 2007). ESC, it is rather linked to the inactivation of RB gene through dysregulation of the p16INK4a/cyclin D-CDK/pRb-E2F pathway (Reid-Nicholson, Iyengar et al. 2006). Reid-Nicholson et al, (Reid-Nicholson, Iyengar et al. 2006) reported that p16 overexpression was detected in 92% (22 of 24) of ESC cases, compared with 7% (3 of 42) FIGO grade 1 and 2 EEC, and 25% (10 of 40) of FIGO grade 3 EEC cases. Unpublished data from our laboratory also show p16 overexpression in lesions

of EmGD and serous EIC (Zheng w et al, unpublished), however, it was also diffusely present in benign endometrial samples, raising the question of the practical relevance of this biomarker in serous carcinogenesis.

### 3.1.5 Differential diagnosis

The diagnosis of serous EIN can be difficult because it does not present as a mass. It may be a focal finding in an otherwise unremarkable endometrial polyp. This is particularly true when a biopsy sample is encountered. The overall clinico-pathologic picture is significant to avoid misdiagnosis (Table 3). The recognition of serous EmGD in an endometrial biopsy or a curettage specimen may aid the pathologist to diagnose serous EIC or to raise concerns for the presence of concurrent ESC before a hysterectomy is undertaken. Attention should be paid in the interpretation of endometrial specimens not to confuse EmGD with any of the following pathologic entities:

#### Reparative epithelial changes in benign endometrium

These benign changes are frequently encountered post -endometrial curettage or biopsy and rarely show the architectural patterns seen in EmGD. The cytologic atypia is minimal. Numerous mitotic figures are lacking as well. In difficult cases, the use of immunohistochemical stains for p53, IMP-3 and ki-67 can be very useful (Figure 11 A &11B).

#### Serous EIC

The most useful criterion here is nuclear atypia, which is marked in serous EIC, even identical to that of invasive ESC. Mitotic figures are also more frequent in EIC.

#### Benign endometrial metaplasias

These may include hobnail metaplasia, papillary metaplasia and also some cases of Arias-Stella reaction. The cytologic atypia in these various types of metaplasia are minimal and they are usually associated with bleeding or breakdown changes in adjacent endometrium. Mitotic activity is rarely seen. Other characteristic cytologic features, such as hobnail nuclei

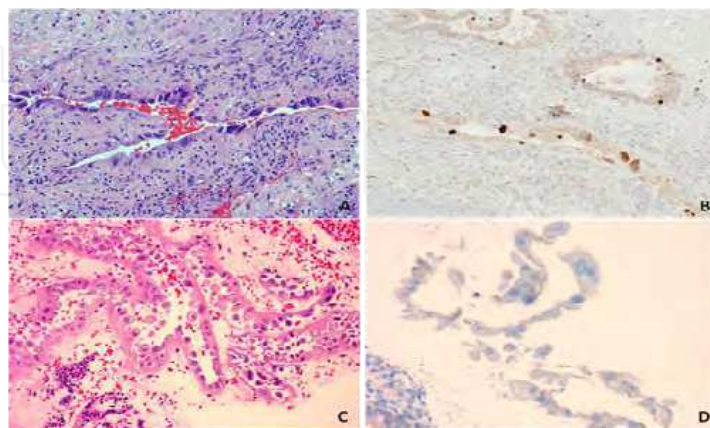


Fig. 11. Reactive endometrial changes. Post-abortive decidulized endometrium may show atypical glandular cells (A), but immunostaining with p53 is weak and focal (B). Hobnail metaplasia in endometrial curettings (C), lack of mitoses and negative p53 stain (D) helps to rule out malignancy.

or cytoplasmic clearing or eosinophilia can further help in the distinction. Pathologic examination should always keep pace with the clinical data and presentation, as a history of a preceding conception or dilation and curettage will help minimize the misdiagnosis of such benign changes with serous EmGD. An example is illustrated in Figure 11C & 11D.

### Endometrial hyperplasia

As previously mentioned, it is of clinical significance to accurately differentiate between the precursors of type I and *type II endometrial cancer*, due to the influence on management and patient outcome. In most of the cases, this should be straightforward, bearing in mind that *type I endometrial cancer* precursors usually lack the highly atypical nuclear features seen in type II precancers, including hobnail appearance, round large nuclei and prominent nucleoli. However, in case of doubt, correlation with positive immunohistochemical stains for p53, IMP-3 would help diagnose *type II endometrial cancer* precancers.

### 3.1.6 Clinical significance and future management

At present, there are no standard management guidelines for patients with EmGD. The approach at our institute is based on our consideration of these patients to be at a significantly higher risk for the development of endometrial malignancy than their counterparts without EmGD, and that this risk is accentuated by factors such as a personal history of breast cancer or BRCA mutations (Chan, Manuel et al. 2006; Liang, Pearl et al. 2010). For patients without breast cancer history and/or BRCA mutations, if the diagnosis of EmGD is confirmed in a biopsy, we recommend complete dilation and curettage (D&C) for larger sampling. If the diagnosis was made on an endometrial curettage, we recommend periodic follow-up (no more than every 6 months) with transvaginal ultrasound and pelvic examinations. The presence of any abnormalities during this period that may be a harbinger for neoplasia, such as persistent abnormal uterine bleeding, abnormal glandular cells on Papanicolaou tests, palpable pelvic masses, or ultrasound abnormalities, should warrant a complete D and C. For those patients with BRCA mutations or a personal history of breast cancer, our gynecologic oncologists typically offer the option for a hysterectomy. Whether or not complete staging is performed would then be dependent on the intraoperative frozen section findings. If a serous cancer is identified, irrespective of its size in representative sections of the uterus, a complete staging, including omentectomy is performed. If no such focus is identified, the procedure is limited to the hysterectomy with or without the salpingoophorectomies. It should be emphasized, however, that additional studies are required to more clearly define the clinical significance of the lesion in everyday practice. This would entail a larger systematic study of endometrial biopsies to establish the time frame between the development of EmGD and ESC, the proportion of EmGD cases that evolve to ESC, and follow-up of prospectively diagnosed cases to confirm that they are never associated with extrauterine disease in a short term.

## 3.2 Clear cell EmGD

### 3.2.1 Historical background

Endometrial clear cell carcinoma (ECCC) is a rare variant of endometrial type II cancer, accounting for 1% to 6% of all endometrial carcinomas cases (Webb and Lagios 1987; Abeler and Kjorstad 1991). It is now established that precursor lesions exist for the more common



and more thoroughly studied types of endometrial cancers, including the spectrum of atypical hyperplasia and classic (endometrioid) EIN for *type I endometrial cancer* (Kurman, Kaminski et al. 1985; Mutter 2000; Mutter 2002; Mutter, Zaino et al. 2007; Scully RE 1994); and serous endometrial glandular dysplasia (EmGD) for ESC (Zheng, Liang et al. 2004; Zheng, Liang et al. 2007; Fadare and Zheng 2009; Zheng, Xiang et al. 2011). However, the other rarer and accordingly less studied variants of endometrial carcinoma, including ECCC, has not been the focus of similar searches. A few pioneer studies are mentioned in the following sections.

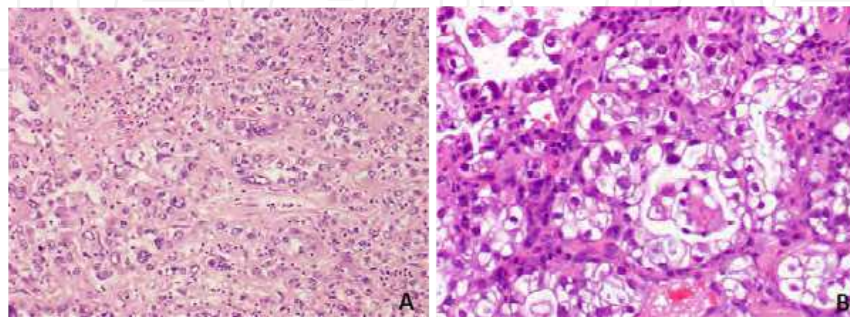


Fig. 12. Clear cell carcinoma of the endometrium.

### 3.2.2 Putative precursor for endometrial clear cell carcinoma: Clear cell EmGD

In 2004, Moid and Berezowski (Moid and Berezowski 2004) described a distinctive lesion in a hysterectomy specimen from a 70-year-old woman which they designated endometrial intraepithelial carcinoma, clear cell type (EIC, clear cell type). The lesion comprised surface epithelium and glands that were lined by cells with “clear cytoplasm, marked nuclear pleomorphism, coarse chromatin, irregular nuclear membranes, and prominent eosinophilic nucleoli” and an occasional hobnail appearance. No mitotic figures were recognized. There was no evidence of stromal or myometrial invasion. The lesions showed “focal” staining for p53, a “moderate to high proliferative index,” and no evidence of extrauterine extension. In 2006, our group studied the characteristic clinicopathologic features of these putative precursor lesions (Fadare, Liang et al. 2006). 14 cases of pure ECCC and 16 endometrial carcinomas with a greater than 10% clear cell component were evaluated, the adjacent benign endometria were searched for lesions that were morphologically distinct from the background benign endometrium and which were not clearly classifiable as a non-neoplastic process. A total of 38 benign uteri and 30 uteri with EEC served as the control groups. In 90% of cases, we identified a spectrum of atypical endometrial glandular and surface changes that were distinct from both the background benign endometrium and the adjacent ECCC. These changes were not identified in any of the control group cases. Transition from resting endometrium to clear cell EmGD, or from clear cell EmGD to clear cell EIC, was detected in 11 (41%) of 27 cases (Fadare, Liang et al. 2006). These morphological changes were also maintained by immunohistochemical stains, which showed that the clear cell EmGD lesions had p53 staining scores and MIB1 proliferative indices that were intermediate between the resting endometrium in which they were identified and the adjacent ECCC. The lesions also showed markedly reduced frequency of ER and PR expression compared with the background endometrium. According to our findings, we hypothesized that these lesions represent precancerous lesions of ECCC. There has been an

inadequate number of cases described to know if clear cell EIC in isolation, like serous EIC, has any capacity or propensity for extrauterine extension. Additional studies, as have previously been carried out on serous EmGD (Zheng, Liang et al. 2007; Zheng, Xiang et al. 2011), are required to conclusively establish the precancerous nature of these per National Cancer Institute criteria (Berman, Albores-Saavedra et al. 2006).

### 3.2.3 Morphologic features of clear cell EmGD

The features of clear cell EmGD are a spectrum of morphological changes involving a single gland, a few glandular clusters or surface epithelium lined by cells with cytoplasmic clarity or eosinophilia, or hobnail nuclei, and varying degrees of nuclear atypia. These changes were graded on a scale of 1 to 3 (Fadare, Liang et al. 2006), primarily depending on the level of cytologic atypia of the constituent cells. A lesion is grade 1 if there is nuclear enlargement (2- to 3-fold compared with resting endometrium) (Figure 13). Grade 3 nuclei show marked pleomorphism and prominent nucleoli comparable to frank ECCC (Figure 12). Grade 2 changes display intermediate features. Mitotic figures were rare in grade 1 and 2 lesions but were easily seen in grade 3 lesions. Morphologically and conceptually, grade 3 lesions were classifiable as clear cell EIC, whereas grade 1 and 2 lesions were designated clear cell endometrial glandular dysplasia (clear cell EmGD).

### 3.2.4 Molecular alterations of clear cell EmGD

The genetic aspects of ECCC are not fully understood, and further studies are required to establish the exact pathogenesis of this unusual tumor. The information assembled from previous efforts suggests that the molecular pathogenesis of ECCC is different from that of EEC and ESC, and that the molecular alterations frequently detected in EEC and ESC, including PTEN, K-ras, and TP53 mutations, are not commonly seen in ECCC. Lax et al (Lax, Pizer et al. 1998); noted that a division of ECCC cases display morphologic features suggestive of ESC (ECCC with serous features) and that the latter showed a higher Ki-67 proliferative index than did typical ECCC. Furthermore, ECCC with serous features were associated with serous endometrial intraepithelial carcinoma (EIC) in 50% of cases. In 2004, An et al (An, Logani et al. 2004), studied 16 ECCCs (including 11 pure and 5 mixed cases) for mutations in the PTEN and p53 genes, and for microsatellite instability. These alterations were detected in only a minority of the pure cases, but they were present in the mixed tumors. In addition, in the 2 cases of mixed ECCC/ESC, identical p53 mutations were identified in the 2 histologically distinct parts of the tumor. In one case of a mixed ECCC/EEC, identical p53 and PTEN mutations, as well as microsatellite instability, were identified in the 2 components. The authors concluded that ECCC "represent a heterogeneous group of tumors that arise via different pathogenetic pathways."

As previously noted, molecular alterations that are characteristic of ESC, such as p53 mutations or down-regulation of E-cadherin, may also be seen in ECCC but at a significantly lower frequency (Lax, Pizer et al. 1998; Holcomb, Delatorre et al. 2002; Yalta, Atay et al. 2009). On the other hand, expression of ER and PR is seen at a considerably lower rate in ECCC than is typical of EEC. Other alterations that have been reported in ECCC include decreased expression of the metastasis suppressor CD82 (Kangai-1) and frequent hypermethylation of the stem cell-related transcription factor (SOX2), and up-regulation of

the oncogenesis-related protein HNF-1A. The first 2 of these alterations are considered to be linked to type II cancers in general, rather than ECCC in particular (Wong, Huo et al.). The precise molecular alterations in clear cell EmGD and clear cell EIC are still uncertain and further molecular and genetic studies are necessary to elucidate them.

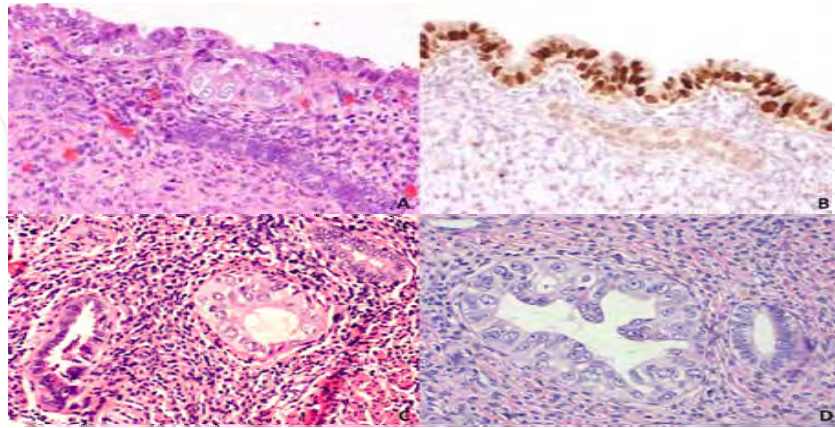


Fig. 13. Clear cell endometrial glandular dysplasia (clear cell EmGD). It can be seen in the surface epithelium (A), or single glands (C&D). Immunohistochemical stain for p53 is positive (B).

### 3.2.5 Clinical significance and future management

Due to limited number of clear cell EmGD cases that have been studied, the practical clinical impact of this diagnosis, especially if it is found in isolation in an endometrial biopsy sample, is simply unclear. Guidelines on how to manage such cases will not be available until more retrospective and prospective studies are done. Clear cell carcinoma is a rare type of endometrial type II carcinoma. Studies of precursor lesions are so far scarce. We previously proposed clear cell EmGD as a putative precursor due to similarities in morphologic and immunophenotypic features of clear cell carcinoma. However, follow-up and molecular studies are required to establish an ancestry connection between the clear cell EmGD, clear cell EIC, and ECCC and to illuminate the genetic pathways involved in the development and progression of these putative precursor lesions.

## 4. Conclusion

Endometrial carcinomas encompass a wide spectrum of morphologically and biologically distinct entities. These can be categorized into 2 major pathways (*type I* and *type II endometrial cancer*) according to the dualistic model of endometrial carcinogenesis. Both types have histologic subtypes, and are distinct in their risk factors, molecular background, precancerous lesions and overall patient outcome. The histologic subtype of endometrial cancer has been demonstrated as a significant prognostic factor. The previously used contradicting nomenclature systems for endometrial precancers had been a basis for confusion and low reproducibility among pathologists. They also resulted in the inappropriate inclusion of certain lesions as precancer lesions that did not qualify as such (e.g. simple hyperplasia without atypia for *type I endometrial cancer*, and serous EIC for *type II endometrial cancer*); which in our opinion makes it essential to search for a more simple and

unified nomenclature system in this context. Based on the previously detailed dualistic model of endometrial carcinogenesis, and with emphasis on the strict criteria of a precancer as defined by the 2006 National Cancer Institute consensus; we believe that endometrioid EIN (as defined by Mutter et al) is the precancer lesion for *type I endometrial cancer*. For *type II endometrial cancer*, on the other hand, our recent studies confirmed that serous EIN (serous EmGD as previously defined) is the precancerous lesion for serous carcinoma. Similarly, clear cell EIN (previously defined as clear cell EmGD) as a putative precancer for clear cell carcinoma. The precancers of type I and type II endometrial cancer are morphologically and biologically distinct entities, and to the best of our knowledge do not overlap or function as precancer of their cancer counterparts. Much is still to be explored regarding the nature, clinical significance, and appropriate management of those precancer lesions. The newly proposed unified endometrial intraepithelial neoplasia classification system, hopefully, will reduce the confusion in clinic and ultimately benefit patients.

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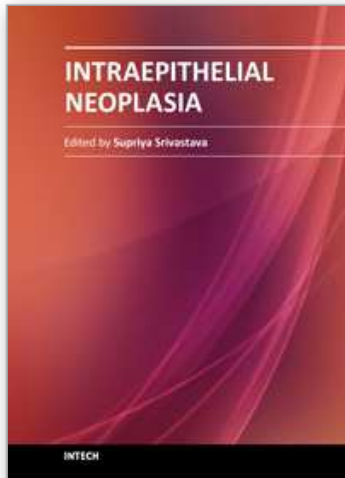
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The book "Intraepithelial neoplasia" is till date the most comprehensive book dedicated entirely to preinvasive lesions of the human body. Created and published with an aim of helping clinicians to not only diagnose but also understand the etiopathogenesis of the precursor lesions, the book also attempts to identify its molecular and genetic mechanisms. All of the chapters contain a considerable amount of new information, with an updated bibliographical list as well as the latest WHO classification of intraepithelial lesions that has been included wherever needed. The text has been updated according to the latest technical advances. This book can be described as concise, informative, logical and useful at all levels discussing thoroughly the invaluable role of molecular diagnostics and genetic mechanisms of the intraepithelial lesions. To make the materials easily digestible, the book is illustrated with colorful images.

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