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Molecular Pathogenesis of Endometrial and Ovarian Cancer

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Abstract

Pregnancy, breastfeeding, and oral contraceptive pill use interrupt menstrual cycles and reduce endometrial and ovarian cancer risk. This suggests the importance of turnover within Mullerian tissues, where the accumulation of mutations in p53 and *PTEN* has been correlated with number of cycles. The most common type of endometrial cancer (Type I) is endometrioid and molecular abnormalities include mutations in *PTEN, KRAS* and β-catenin. The Type I precursor is Endometrial lntraepithelial Neoplasia which displays *PTEN* defects. Type II endometrial cancer (whose precursors are less clear) includes serous and clear cell tumors and the most common alteration is p53 mutation. For ovarian cancer, histopathologic types parallel endometrial cancer and include serous, mucinous, endometrioid, and clear cell; some molecular features are also shared. The most frequent type of ovarian cancer is high grade serous that often displays p53 mutation and its precursor lesions may originate from normal-appearing fallopian tube epithelium that contains a p53 “signature”. Mutations in *KRAS, BRAF* and *PTEN* are described in mucinous, endometrioid and low grade serous cancers and these may originate from ovarian cortical inclusion cysts. A consideration of molecular and other pathogenetic features, like epidemiology and histopathology, may provide a bener understanding of endometrial and ovarian cancer.

Keywords

Ovarian cancer; Endometrial cancer; p53; PTEN; KRAS; Precursor lesions; Endometrial intraepithelial neoplasia; Fallopian tube; Cortical inclusion cysts

I. Introduction

Pathogenesis is a term that implies understanding a disease at many levels, thus requiring knowledge of susceptible populations, etiologic factors, histopathology at the gross and microscopic level, and delineation of precursor lesions. Understanding a disease at these levels should not be abrogated when we focus on “molecular pathogenesis”. Rather, by overlaying an understanding of the process at a biochemical or genetic level, the greatest understanding of the origins of a disease is achieved and has the best chance of translating into methods for prevention or treatment. Thus, in our consideration of the Molecular Pathogenesis of Endometrial and Ovarian Cancer, epidemiologic and histopathologic aspects will be first examined. We are considering endometrial and ovarian cancer together because these gynecologic cancers have many intriguing similarities, which together with some important differences, will be revealed in this chapter.

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2. Epidemiologic “Pathogenesis”

2.1 Age and Geographic Distribution

In the U.S., endometrial cancer is the most common gynecologic cancer accounting for 40,100 new cases and 7,470 deaths [1]. Ovarian cancer accounts for fewer cases (21,650) but more deaths (15,520) [1]. Ovarian cancer is the leading cause of death from a gynecologic cancer and fifth leading cause of cancer deaths overall in the U.S. Endometrial and Ovarian Cancer share similar patterns of distribution by age and geography. Both cancers rise sharply in occurrence during the perimenopausal years and peak after the menopause (Fig I). However, while endometrial cancer rates drop rather sharply after age 65, ovarian cancer rates continue to rise well into a woman's eighties. Worldwide much higher rates of endometrial and ovarian cancer are observed in industrialized and Northern European populations and lower rates in third world countries (Table 1). The correlation between these rates is significant (Pearson correlation = 0.809. $p<0.001$) and associations with per capita fat consumption have been described for both [2-4].

2.2. Risk Factors

As reviewed in Table 2, many shared risk factors for endometrial and ovanan cancer relate to reproductive factors including trends for decreasing risk associated with increasing number of pregnancies, longer duration of breastfeeding, and more years of oral contraceptive (OC) pill use. A late age at menarche decreases risk for both cancers and a late age at menopause increases risk for endometrial cancer, but less clearly so for ovarian. These events can be fit into a composite variable that estimates years of ovulation or, when average cycle length is included, number of ovulatory cycles. Increasing ovulatory cycles clearly correlates with increased risk for ovarian cancer. Though less well studied, ovulatory cycles also appears to correlate with endometrial cancer risk [5].

The link between ovulatory cycles, endometrial, and ovarian cancer illustrates the potential relevance of a consideration of risk factors to molecular pathogenesis. For ovarian cancer, the monthly disruption and repair of the surface epithelium of the ovary is proposed to lead to genetic damage due to the accumulation of mutations of the tumor suppressor, p53, in the ovarian or fallopian tube epithelium [6-9]; but this mechanism would not explain the association with endometrial cancer. One possibility is that “incessant ovulation” largely equates with “incessant menstruation” involving repeated disruption and re-growth of the uterine lining. A greater number of cycles of endometrial regeneration may increase the likelihood of random genetic mutations because DNA replication errors occur during cell division, and thus are more likely to occur in tissues undergoing many cell divisions. Estimates of the rate of sporadic mutagenesis in human cells, on the order of 10^{-7} mutations per gene per cell division [10] suggest that the number of cells with “first hits” on a multistep carcinogenesis pathway [11, 12] may number in the hundreds for every gram (10^9 cells/gram) of proliferative tissue. It is no surprise, then, to find that sporadic mutations of another tumor suppressor gene, *PTEN,* are observed in almost half (43%) of histologically normal endometria of naturally cycling premenopausal women [13].

Another risk factor for endometrial and ovarian cancer is menopausal hormone use, especially of estrogen only forms unopposed by a progestin, although the magnitude of this effect is greater in endometrial cancer. Medical conditions which may relate to risk for both types of cancers include high body mass index and polycystic ovarian syndrome (PCOS). High body mass index (BMI) is a well-established risk factor for Type 1 endometrial cancer and has been linked to elevated levels of estrogen, particularly in post-menopausal women where adipose tissue is the main site of estrogen production from androgen precursors [14]. High BMI also appears to be associated with increased ovarian cancer risk through similar

hormonal mechanisms, although the link is not as well established [15, 16]. PCOS, a condition characterized by ovarian hyperandrogenism, chronic anovulation and progesterone deficiency, has also been associated with both ovarian and endometrial cancer [17-19].

Several familial syndromes are associated with increased risk of endometrial and ovarian cancer. The most well-known germ line mutations that predispose to ovarian cancer involve the *BRCA1* and *BRCA2* genes. It has been estimated that mutations in *BRCA1/2* might account for up to 10% of all ovarian cancer cases [20]. The risk of endometrial cancer does not appear to he significantly elevated in *BRCA1/2* mutation carriers in general, however among the subgroup of women who used tamoxifen for treatment or primary prevention of breast cancer, risk of endometrial cancer was significantly elevated (Relative Risk = 11.6, p=0.004) [21]. A familial autosomal dominant syndrome characterized by defective DNA mismatch repair, Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is associated with a 40-60% and 8-15% increased lifetime risk of endometrial and ovarian cancer, respectively [22, 23]. Another autosomal dominant disorder that has been suggested to predispose to endometrial cancer development is Cowden's Syndrome, in which 13 - 80% of patients have a germ line mutation of *PTEN* [24, 25]. However Cowden's Syndrome likely accounts for a very small propottion of endometrial cancer cases when viewed against somatic *PTEN* mutations observed in sporadic cases [26]. Patients with Cowden's Syndrome may also present with benign ovarian cysts and teratomas but generally not malignant ovarian neoplasms [24].

There are other shared risk factors between endometrial and ovarian cancer that are surprising and raise intriguing questions related to pathogenesis. IUD use, even hormonally inert types, clearly decrease the risk for endometrial cancer [27, 28] and some studies suggest these may also decrease the risk for ovarian cancer [29, 30]. Similarly, tubal ligation is a strong protective risk factor for ovarian cancer that may also decrease the risk for endometrial cancer [31-34]. Current smoking is associated with reduced risk of endometrial cancer, particularly in postmenopausal women, possibly due to the anti-estrogenic effects of smoking such as reduced body weight, lower age at menopause and differences in estrogen metabolism [35]. Current smoking has also been associated with decreased risk of clear cell ovarian tumors, however no association was observed with serous and endometrioid tumors and smoking doubled the risk of mucinous ovarian cancers [36]. Talc use, another factor found to consistently increase the risk for ovarian cancer [37-40] has not yet been investigated for endometrial cancer.

In summary, this brief review of epidemiologic risk factors reveals a surprising number of similarities in endometrial and ovarian cancers which suggests that there may also be shared mechanisms in their molecular pathogenesis.

3. Histopathology

3.1 Endometrial cancer

The histopathologic categories of endometrial cancer, identified by their unique microscopic features, include endometrioid (most common), serous and clear cell as well as the rarer subtypes mucinous, squamous, transitional cell, carcinosarcoma and undifferentiated tumors (Table 3). Although endometrial cancers exhibit a variety of histologic features, >95% can be classified into two clinicopathologic groups, endometrioid (Type I) and non-endometrioid (Type II) [41, 42].

3.1.1 Endometrial Adenocarcinoma, Endometrioid Type (Type I)—The majority (70-80%) of endometrial cancers are classified as Type I tumors. Most Type I tumors are described as endometrioid and exhibit a resemblance to benign endometrium. Other

histologic variants include mucinous tumors that resemble the endocervix and adenosquamous tumors that display keratinization (43). Type I tumors are influenced by endocrine modulation (estrogen unopposed by progesterone) and generally follow an indolent clinical course. These tumors are better differentiated with mild to moderate nuclear pleiomorphism and show less myometrial invasion and low potential for lymphatic spread [44].

3.1.2 Endometrial Adenocarcinoma, Non-Endometrioid Type (Type II)—Type II tumors are typically characterized by serous or clear cell histologies, or the very poorly differentiated phenotypes of carcinosarcoma or undifferentiated carcinoma [45]. They are not associated with clinical evidence of estrogen stimulation, exhibit low sensitivity to progestin and typically arise in the setting of an atrophic endometrium. They have a high degree of nuclear pleomorphism [46, 47], exhibit deeper myometrial invasion, are at higher risk of lymphatic spread and are associated with a more aggressive clinical course [48, 49].

3.2 Ovarian Cancer

Ovarian malignancies may arise from germ cell, stromal, or epithelial compartments. Approximately 25% of ovarian tumors, including benign neoplasms, are of germ cell origin and the most common is the mature teratoma (dermoid) which accounts for nearly 1/3 of benign ovarian neoplasms [50]. Only 2-3% of germ cell tumors are malignant and these include rare types such as dysgerminomas, endodermal sinus tumors and embryonal carcinomas [50]. Ovarian stromal tumors account for 6% of all ovarian tumors and include neoplasms derived from the sex cords and specialized stroma of the developing gonad [50]. Stromal tumors may arise from female-type (granulosa, theca) and male-type cells (Sertoli, Leydig) as well as other indifferent sex cord derivatives. Some of these tumors are hormonally active; benign thecomas are known for their estrogen production while Sertoli-Leydig cell tumors recapitulate testicular structures and may have virilizing properties [51]. The most common stromal tumor is the granulosa cell tumor which accounts for approximately 10% of ovarian cancers.

By far the most common types of malignant ovarian cancers are epithelial which tend to parallel the same types arising in the endometrium (Table 4). Four major histologic subtypes of epithelial ovarian cancer have been described, with each resembling different types of epithelia in the female reproductive tract [52]. Features associated with fallopian tube, endocervical or endometrial epithelia are observed in serous, mucinous and endometrioid forms of ovarian cancer, respectively. Clear cell tumors are the fourth major histological subtype and are identified by clear, peg-like cells that resemble the lining of the endometrial glands during pregnancy. The majority of malignant ovarian tumors fall into the invasive serous category followed by endometrioid, clear cell and mucinous types.

A distinction made for ovarian cancer that does not have an exact parallel in endometrial cancer is the designation of “borderline” or “low malignant potential” ovarian tumor types that may spread beyond the ovary yet have an indolent course. While all of the tumor types described in Table 4 have a malignant counterpart, generally the low malignant potential tumors have serous or mucinous histopathology while low malignant potential endometrioid and clear cell tumors are rarely observed [50].

An anempt has been made to apply a dichotomous low *vs* high grade stratification to cancer of the ovary [53, 54], as the underlying genotypic findings and associated clinical outcomes fall into two distinct groups. This model is a starting point to make diagnostic classifications that are concordant with ovarian cancer pathogenesis, but is not as useful as the Type I and II distinction developed for endometrial cancer. Thus, there is a low grade category of tumors that tend to arise in a stepwise manner from borderline tumors, and may have serous

or mucinous histologies. These tumors generally exhibit lower rates of cell proliferation, a gradual increase in chromosomal instability and a less aggressive clinical course. The most common type is low grade serous carcinoma and 25% of all serous carcinomas fall into this category. In contrast, high grade tumors are generally serous histology and exhibit widespread chromosome instability, tend to develop rapidly, metastasize early and are associated with a poor prognosis.

4. Molecular Pathogenesis – General Aspects

Features that describe the molecular pathogenesis in a cancer include large scale genomic changes as well as mutations or alterations in specific genes or pathways. The main mechanisms responsible for large scale genomic changes in tumor cells are microsatellite instability (MSI) or chromosome instability (changes in DNA copy number) [55]. MSI is often a direct result of defective mismatch repair mechanisms and can be identified by replication errors in repeated units of 1-4 DNA base pairs (microsatellites) that are distributed throughout the genome [56]. In endometrial cancer, MSI most often occurs from epigenetic silencing and inactivation of the MutL Homolog 1 *(MLH1)* gene through hypermethylation of CpG islands in its promoter region [57]. This form of genetic instability increases the mutation rate and can accelerate the acquisition of further generic damage that may lead to carcinogenic transformation.

Chromosome instability reters to chromosomal modifications such as gains, losses or rearrangements that may lead to oncogene activation or rumor suppressor inactivation. Chromosome instability can be detected cytogenetically using techniques like conventional karyotyping, in which metaphase spreads of human chromosomes are analyzed, or fluorescence *in situ* hybridization (FISH) in which specific chromosomes or loci are marked by fluorescent probes. Comparative genomic hybridization (CGH) assesses genomic imbalance and provides a measure of gene amplication and deletion.

Allelic imbalance (AI) is another type of chromosome instability where one allele of a gene is lost or amplified. Loss of heterozygosity (LOH) is a common form of AI and refers to the situation where one chromosome has a normal allele of a gene and the other has a mutant or deleted allele. If one allele is already inactivated then only a second inactivating hit may be required, which has particular relevance for tumor suppressor genes [55]. A method commonly applied to estimate genome-wide AI is the Single Nucleotide Polymorphism (SNP) array which measures the number of SNP markers with allelic imbalance divided by the total number SNP markers.

Inactivating mutations of specific genes generally involve base substitutions, deletions or insertions of only a few nudeotides and consequently these are often detected by direct sequencing of the gene of interest in the genomic DNA. As DNA sequencing can be labor intensive, immunohistochemical stains have been developed that allow the detection of well-studied genes, such as somatic *PTEN* mutation in endometrial cancer, so that gene mutation can be inferred based on positive or negative staining in formalin-fixed paraffin-embedded tissues.

The spectrum of genes affected in cancer can be wide and varied and some genes and pathways are involved in a variety of cancers. This is true for endometrial and ovarian cancer where several common genes and pathways have been described. A large amount of research has focused on p53 after it was discovered that the tumor suppressor gene *TP53* is frequently mutated in a high proportion of human cancers [58]. Activation of p53 normally occurs in response to DNA damage, aberrant proliferative growth signals, and carcinogenic factors such as exposure to UV radiation [59]. Activated p53 carries out several functions, of

which the most comprehensively understood are its ability to cause cell cycle arrest at the G2/M DNA damage checkpoint and to induce apoptosis [60, 61].

Mutations in *KRAS* and *BRAF* that cause aberrant activation have been identified in both endometrial and ovarian cancer and appear to play a central role in carcinogenesis by conducting signals that enhance cell proliferation during tumor development [62, 63). RAS, a small GTP binding protein, activates the core unit of a cascade composed of RAF, mitogen/extracellular signal-regulated kinase (MEK1/2) and MAP Kinase (MAPK or ERK) as well as the PI3K/ AKT pathway [64-66].

Inactivating mutations of the tumor suppressor gene, *PTEN,* are detected in both endometrial and ovarian cancer, *PTEN* is an inhibitor of PI3K/ AKT signaling and acts to control the rate of cell division and promote apoptosis [67]. Loss of *PTEN* may occur through a variery of mechanisms, however the most common is inactivation of both alleles through mutation or deletion in combination with LOH at chromosome 10q23 to generate a protein deficient state with a complete loss of function phenotype [68, 69].

Gain of function mutations of the *CTNNB1* gene (β-catenin) are identified in endometrial and ovarian cancer [70-73], especially those with squamous differentiation. These mutations stabilize the β-catenin protein in the cell cytoplasm and nucleus which leads to activation of the lymphoid enhancing binding factor (LEF) and T cell-specific transcription factor (TCF) pathways that promote transcription of target genes involved in tumorigenesis such as *C-MYC* and *COX2* [74, 75].

5. Molecular Pathogenesis of Endometrial Cancer

5.1 Type I Endometrial Cancer

Type I endometrial cancers display a wide range of genetic alterations which differ in their temporal sequence and cumulative combinations between patients. MSI is reported in approximately 20% of Type I endometrial cancers of all grades [76-79], however since the majority of endometrioid carcinomas do not exhibit MSI this is not a necessary, or even predominant, feature of endometrial carcinogenesis [43]. More common changes include specific alterations such as *PTEN* inactivation and aberrant activation of *KRAS* and β-catenin.

The most common genetic alteration in Type I endometrial cancer is *PTEN* inactivation. The proportion of endometrial cancers that demonstrate *PTEN* inactivation varies by case selection, with the highest rates (83%) observed in sporadic cases associated with a coexisting or prior premalignant lesion [80]. Furthermore, the functional role of *PTEN* in Type I endometrial cancer development has been demonstrated in *PTEN* knockout mice where 20% developed endometrial cancer [81].

Mutations in *KRAS* causing aberrant activation have been implicated in 10-30% of Type I endometrial cancers [82-84]. Gain of function mutations in exon 3 of the *CTNNB1* gene (β-catenin) are also observed in 25-38% of Type I cancers [70, 71, 85]. Interestingly, MSI, *PTEN* and *KRAS* mutations frequently coexist with in the same tumor, however these molecular alterations are not usually seen in combination with β-catenin mutation (86). Hence, it has been suggested that Type I endometrial cancers with β-catenin mutations may develop via a unique pathway that includes a change in differentiation state towards a squamous morphology [87. 88].

In contrast to the more common genetic alterations discussed above, aberrant accumulation of inactive p53 protein is observed in only 5% of Type I endometrial cancers [82]. Furthermore, the mechanism of p53 inactivation differs between Types I and II tumors; in

Type I tumors aberrant p53 protein accumulation results from changes in upstream regulatory proteins, such as MDM2 and p14 ARF, while Type II tumors often have p53 truncation mutations [89-91] as discussed below.

5.2 Type II Endometrial Cancer

Type II endometrial cancers demonstrate genetic instability at the chromosome level resulting in a high level of aneuploidy while maintaining intact MMR [46, 47, 92]. The primary genetic defect is mutation of the p53 gene, observed in 75-100% of tumors [44, 93]. One preliminary study has reported that levels of aberrant p53 expression in clear cell carcinoma may be intermediate between those reported in papillary serous carcinoma and endometrioid tumors [94]. Both papillary serous and clear cell carcinoma have low expression of estrogen and progesterone receptors [44]. Amplification or overexpression of HER2 has also been reported in 20% of Type II endometrial cancers [95-98]. In contrast with Type I tumors, inactivation of *PTEN* and *RAS* activation is not observed [44].

5.3 Precursor Lesions of Endometrial Cancer

The immediate precursor lesion for Type I endometrial cancer is known as Endometrial Intraepithelial Neoplasia (EIN) which in turn is presumed to arise from “latent precancers”, or otherwise normal appearing endometrial glands that exhibit somatically acquired mutations in *PTEN* (Fig 2). *PTEN* mutations can be detected by immunohistochemical staining in paraffin embedded tissues [13] but are not associated with cytologic or architectural abnormalities and therefore cannot be detected using routine diagnostic methods [43]. The frequency of occurrence of *PTEN* deficient latent precancers is extremely common, occurring in up to 43% of normal premenopausal women [13]. This high prevalence suggests that the rate of progression from the latent precancer stage to an adenocarcinoma is relatively low, since lifetime endometrial cancer risk is only 2.6% [99].

There is strong evidence to support the transition from EIN to a Type I endometrial adenocarcinoma. First, one third of patients diagnosed with EIN have a concurrent occult carcinoma, and those that are initially cancer free have a 45-fold increased risk of endometrial cancer as compared with patients diagnosed with endometrial hyperplasia without EIN [100]. Second, a similar repertoire of genetic alterations have been identified in EIN and adenocarcinomas and, within the same patient, specific *PTEN,* MSI and X chromosome inactivation patterns are observed in both areas of EIN and adenocarcinoma [78, 101]. While EIN and adenocarcinomas share many characteristics, adenocarcinomas differ in that they exhibit a greater cumulative mutational load as would be expected during carcinogenic transformation. For example, inactivation of *PTEN* is found in *55%* of EIN lesions and 83% of adenocarcinomas which followed the same EIN lesion [80, 102]. Similarly, the proportion of altered microsatellite alleles increases from EIN to carcinoma [78, 101]. Interestingly, no markers have been identified that are uniquely present in adenocarcinomas compared with EIN [103].

Hormonal mechanisms have been integrated into the model of Type I endometrial carcinogenesis. The influence of estrogens can be implicated at the very earliest stages, acting upon *PTEN* defective latent precancers and EIN lesions. Both have been shown to maintain high levels of nuclear estrogen and progesterone receptors [13] and under conditions of estrogen stimulation it is hypothesized that *PTEN* defective cells would have a selective proliferative advantage since *PTEN* would not carry out its normal role to limit the rate of cell division [103].

With the knowledge that *PTEN*-null clones are present at a high frequency in “ normal” women, and that these (83%) are usually retained for at least one years duration [13], this

provides a genetically predisposed cell population that is a target for, and effector of, hormonal risk modulation. This approach has been applied in a recent study that directly observed the effects of risk-modifying factors on latent precancers in the endometrium using *PTEN* inactivation within normal appearing tissues as the biomarker [104]. The risk-modifying factors examined were use of hormonally-inert mechanical intrauterine devices (IUDs) or low dose combined oral contraceptive (OC) pills, which confer a 40% and 50% reduction in risk, respectively, compared with controls [28, 105, 106]. It was shown that women with a history of IUD or OC pill use had a lower rate of latent endometrial precancers detected by *PTEN* immunohistochemistry and the magnitude of latent precancer decline was proportionate to the extent of diminished endometrial cancer risk as previously determined by epidemiological studies [104]. This data therefore supports a model in which long-term outcome (e.g. endometrial cancer risk) can be altered by interventions at an early susceptible moment.

Less is known about early events in Type II endometrial carcinogenesis as compared with Type I. This results in part from the rarity of papillary serous endometrial cancers compared with their endometrioid counterparts and the probable rapid emergence of a papillary serous carcinoma from an apparently normal state with a small window for clinical detection of early disease [43]. Two putative precursor lesions have been proposed for papillary serous disease, serous intraep ithelial carcinoma (serous EIC) [107, 108] and endometrial glandular dysplasia (EGD) [109] (Fig 2).

Serous EIC is a noninvasive form of papillary serous adenocarcinoma [110]. EIC is observed in approximately 90% of uteri with invasive papillary serous carcinoma and usually presents as an extension from the co-existing invasive carcinoma [107]. EIC exhibits p53 mutation and cytologic features similar to that observed in serous adenocarcinoma [43]. Serous EIC has rarely been reported as the initial diagnostic manifestation of a non-invasive papillary serous adenocarcinoma [111]. Rather, instances where isolated EIC can metastasize to peritoneal and abdominal sites have been reported [112] and in this case serous EIC should not be classified as “premalignant” but rather would be an immediate precursor to invasive disease.

EGO has been identified in uteri of up to 53% of patients with invasive or noninvasive papillary serous carcinoma [43]. EGO displays a histology and genotype that is intermediate between normal endometrium and serous carcinoma. Specifically, it lacks the cytologic atypia of serous EIC, has moderate abnormalities of p53 and lower mitotic activity [109]. Further molecular analysis identified progressive allelic loss within individual patients from EGO to serous carcinoma [113]. Although this lesion has promise as a putative precursor lesion, the frequency of occurrence is unknown outside of a cancer context and the histologic phenotype is not readily identifiable as it can be easily confused with reactive changes [43]. Further studies are needed to learn more about these putative precursor lesions for Type II endometrial carcinoma and to determine the potential clinical implications for patient management.

6. Molecular Pathogenesis of Ovarian Cancer

6.1 Serous low grade tumors

The most common molecular genetic changes that distinguish serous low grade from serous high grade ovarian tumors are alterations in the MAPK signaling cascade, specifically mutations in *KRAS* or *BRAF*. Activating mutations in *KRAS* have been observed in 30-50% of serous borderline and low grade serous carcinomas, but rarely in high grade serous cancers [54, 114, 115]. *BRAF* mutations are found in 28 and 30% of borderline or low-grade serous carcinomas, respectively [115]. Neither *KRAS* nor *BRAF* mutations are

found in high grade serous carcinomas. Interestingly, *KRAS* and *BRAF* mutations are mutually exclusive and rarely found with in the same tumor, which supports the hypothesis that mutation of only one is sufficient to activate the MAPK pathway [115].

Studies of allelic imbalance (AI) showed a progressive increase in the degree of AI from a borderline tumor to a low grade serous carcinoma [54]. This contrasts with high grade serous carcinomas which show a high level of AI (and correlated chromosomal instability), even at their earliest clinical stages [53]. In addition, serous borderline and low grade tumors exhibit a similar low level of chromosomal imbalance (measured from CGH analys is) as compared with high grade serous carcinoma [116, 117). MSI does not appear to be a characteristic of serous borderline tumors [118] and p53 mutation is rarely detected [53]. In combination, these data support the likely progression of serous borderline tumors to low grade serous carcinoma and an apparent separate pathway to development for serous high grade tumors.

6.2 Serous high grade carcinoma

The most common genetic alteration in serous high grade carcinoma is p53 mutation, found in 50-80% of advanced stage, high grade, serous carcinomas [119]. In addition to p53 mutation, these tumors demonstrate amplication/ overexpression of HER2 in up to 70% of cases which is rare in other tumor subtypes [120, 121].

Amplification of either *PIK3CA* or *AKT2* was observed in 27% of high grade serous carcinomas but not serous borderline tumors [122]. Furthermore, application of a Single Nucleotide Polymorphism (SNP) array identified widespread DNA copy number changes in high grade serous ovarian carcinomas that were not apparent in low grade serous tumors, such as alterations in loci harboring candidate the oncogenes cyclin El *(CCNE1), AKT2, Notch3* and *PIK3CA* [123].

Serous high grade tumors are characterized by an increased cell proliferation (Ki-67) index [124] as well as high level genomic instability measured as chromosome and allelic imbalance [54, 116, 117]. These tumors rarely have *KRAS* and *BRAF* mutations which suggests that they develop via a pathway that is unrelated to RASfRAF/MEKIMAPK signaling [125].

It has been difficult to identify morphologically recognizable precursor lesions for high grade serous carcinoma as these tumors usually present at an advanced stage. Two hypotheses have been proposed to explain their origin: these tumors develop ‘de novo’ from the ovarian surface epithelium or its Mullerian inclusion cysts [126] or, alternatively, the fallopian tube fimbria may be the site of origin of a population of malignant tubal cells that exfoliate and grow rapidly upon seeding ofthe ovary [127, 128] (discussed further in Pathway III below).

6.3 Mucinous tumors

The most common molecular feature of mucinous tumors is a high prevalence of *KRAS* mutations, generally found in codon 12. Mutation frequencies of 13%, 33-63% and 50% have been described for cystadenomas, borderline tumors and carcinomas, respectively [129-131]. Furthermore, *KRAS* mutations were identified in both intestinal and endocervical types of benign and borderline mucinous tumors [130, 132, 133].

Another molecular marker that was recently identified in borderline and invasive mucinous ovarian neoplasms is *CEACAM6,* however it remains to be determined whether this is a general marker for mucinous differentiation or a potential key player in carcinogenic

transformation [134]. Other molecular genetic changes such as MSI and p53 mutation, have rarely been reported in mucinous tumors [53, 135].

It has been hypothesized that both serous low grade and mucinous low grade tumors develop in a stepwise manner from well-recognized precursors, namely borderline tumors that may in turn develop from cystadenomas and adenofibromas [136, 137]. Molecular evidence that supports this hypothesis is the identification ofthe same *KRAS* mutation in benign, borderline and malignant portions of the same tumor [132, 133, 138] and the gradual increase in chromosome instability observed in benign, borderline and malignant tumors [53]. The majority of benign epithelial ovarian tumors are of the serous and mucinous subtype [136] and it is generally accepted that the ovarian surface epithelium or its Mullerian inclusion cysts are a common site for the initiation of serous low grade and mucinous ovarian carcinogenesis [53, 139].

6.4 Endometrioid and clear cell carcinoma

Endometrioid and clear cell carcinomas are unique from serous and mucinous tumors in that a proportion (13-50%) exhibit MSI [72, 140, 141]. Specific molecular alterations that characterize endometrioid ovarian tumors are mutations of β-catenin [72, 73] and *PTEN* [142] in one third and 20% of cases, respectively. These mutations are detected in well differentiated, stage 1 tumors and thought to be an early event [53]. *KRAS* mutations have also been identified in endometrioid tumors albeit at a lower frequency (<10%) [143].

Ovarian clear cell carcinomas are relatively rare and consequently little is known about molecular mechanisms involved in tumor development [53, 144]. Based on preliminary studies, *PTEN* mutation has been repotted in 8-40% of cases [145, 146] and mutation of the TGF-β receptor II was detected in three cases [147]. Overexpression of hepatocyte nuclear factor-1 β at the mRNA and protein level has also been observed in clear cell but not other tumor subtypes [148, 149]. Mutations in p53 have rarely been detected in endometrioid and clear cell tumors [53].

In contrast to the putative pathway to development of mucinous or low grade serous carcinoma, benign and borderline endometrioid and clear cell tumors are rarely reported [52]. Rather, it has been proposed that both endometrioid and clear cell carcinomas may arise from endometriosis implanted on the ovary [53, 150, 151]. Evidence is strongest for the endometriosis to ovarian endometrioid carcinoma progression as similar molecular alterations, specifically LOH at 10q23 (the location of *PTEN*) and *PTEN* mutation, were identified in endometriosis, atypical endometriosis and ovarian endometrioid carcinoma in the same patients [142, 145, 152). In addition, functional evidence linking endometriosis and endometrioid ovarian cancer is provided by a mouse model where tissue-specific expression of active mutant *Kras* resulted in pe lvic endometriosis, and expression of active mutant *Kras* in combination with *Pten* inactivation caused metastatic endometrioid ovarian carcinoma that resembled human disease [153].

Clear cell ovarian cardnoma is frequently observed in association with endometriosis, however molecular evidence to support a stepwise progression is not available due to the lack of specific markers for this tumor type [53]. Although there is good evidence that endometriosis is a precursor for at least some ovarian endometrioid and clear cell tumors, further biological evidence is needed to support a causative link in human studies.

6.5 Precursor lesions of ovarian cancer

Based on the data currently available, we propose a model to summarize the pathogenesis of the distinct subtypes of ovarian cancer that accounts for the different putative cells of origin for this disease (Fig 3).

6.5.1 Pathway I (Serous low grade and Mucinous)—begins in the ovary or within Mullerian inclusion cysts (MICs) in the majority of cases. MICs may form when the ovarian surface or other epithelium (such as salpingeal) becomes entrapped after ovulation or by surface adhesion. MICs have been the classic explanation for the origin of benign serous and mucinous cystadenomas, some of which may progress through borderline serous and mucinous counterparts and onto carcinomas.

6.5.2 Pathway II (Endometrioid and Clear Cell)—describes the origin of ovarian cancer from endometriosis derived from transport and implantation of endometrial cells from the uterus [154, 155]. An origin of endometrioid differentiation directly from MICs is also possible since many endometrioid carcinomas are not clearly associated with endometriosis.

6.5.3 Pathway III (Serous high grade)—may arise anywhere in the pelvis, but the fallopian tube is now the best documentted, and most frequent, site of origin. Such tumors are typically detected after bulky peritoneal and ovarian surface involvement has already emerged. For decades, the initial disease focus in the distal fallopian tube has been missed because of its small size and lack of thorough pathologic examination at that site [156]. Epithelial cells prominent at the distal (fimbriated) end of the tubes may undergo repetitive cyclic changes during ovulatory cycles and be subject to genotoxic stresses that lead to DNA damage and p53 mutation accompanied by high cell proliferation rates and poor prognosis [7]. Women who carry BRCA mutations may be especially vulnerable to develop tubal intraepithelial carcinoma which may give rise to high grade serous cancers. Data that supports this hypothesis includes the involvement of the fallopian tubes in a high proportion (42-100%) of BRCA1/2 cancers and frequent identilication of hyperplasia and/or potential pre-neoplastic lesions (p53 positive cells) in prophylactic salpingectomy specimens [8, 157]. Furthermore, a microarray-based study demonstrated that normal fallopian tube had a more similar RNA expression prolile to serous carcinoma as compared to normal ovarian epithelial, endometrial and colon specimens [158]. A recent epidemiological study also found that serous ovarian and fallopian tubes cancers exhibited similarities in risk factor profiles [159]. Fallopian tube cancers are morphologically indistinguishable from high grade serous ovarian cancers and likely should be considered the same disease from a pathologic, clinical and epidemiologic standpoint.

In summary, the evidence base developed in the last 5 years supporting a tubal origin for serous high grade ovarian cancers is now much stronger than the cumulative data of several decades investigating ovarian inclusion cysts as the site of origin. Although it is likely that both tubal and non-tubal sites of origin for high grade serous carcinoma occur, the fallopian tube appears to be more common. Further studies are needed to identify the molecular pathways that may be involved in the carcinogenic transformation ofthe putative cells of origin for high grade serous ovarian carcinoma.

7. Conclusion

This review has highlighted similarities in endometrial and ovarian cancer that includes highly correlated incidence rates, similar risk factor profiles and several common genes and pathways involved in their molecular pathogenesis. Analyses of different histologic subtypes identifies common microscopic features in serous and endometrioid types, regardless of the organ of origin. Furthermore, serous tumors are characterized by defects in p53 and endometrioid tumors are associated with mutations in *PTEN* or β-catenin regardless of the primary organ site. On the other hand, similar mutations may be associated with distinct histopathologies, for example in the endometrium *KRAS* mutation is associated with endometrioid histology while in the ovary *KRAS* mutations are more common in mucinous

and low grade serous cancers. For clear cell cancers the case is less clear. Similar gene expression profiles associated with clear cell differentiation have been identified regardless of whether the tumor originated in the endometrium or ovary [160], however the molecular pathogenesis of clear cell tumors appears quite distinct, with clear cell endometrial tumors showing defects in p53 while clear cell tumors of the ovary have *PTEN* mutation and p53 mutation is rare. In conclusion, the molecular pathogenesis of ovarian and endometrial cancer is best appreciated by an understanding of the epidemiology, histopathology and molecular features. In combination, these approaches may provide the best opportunity for prevention and early detection.

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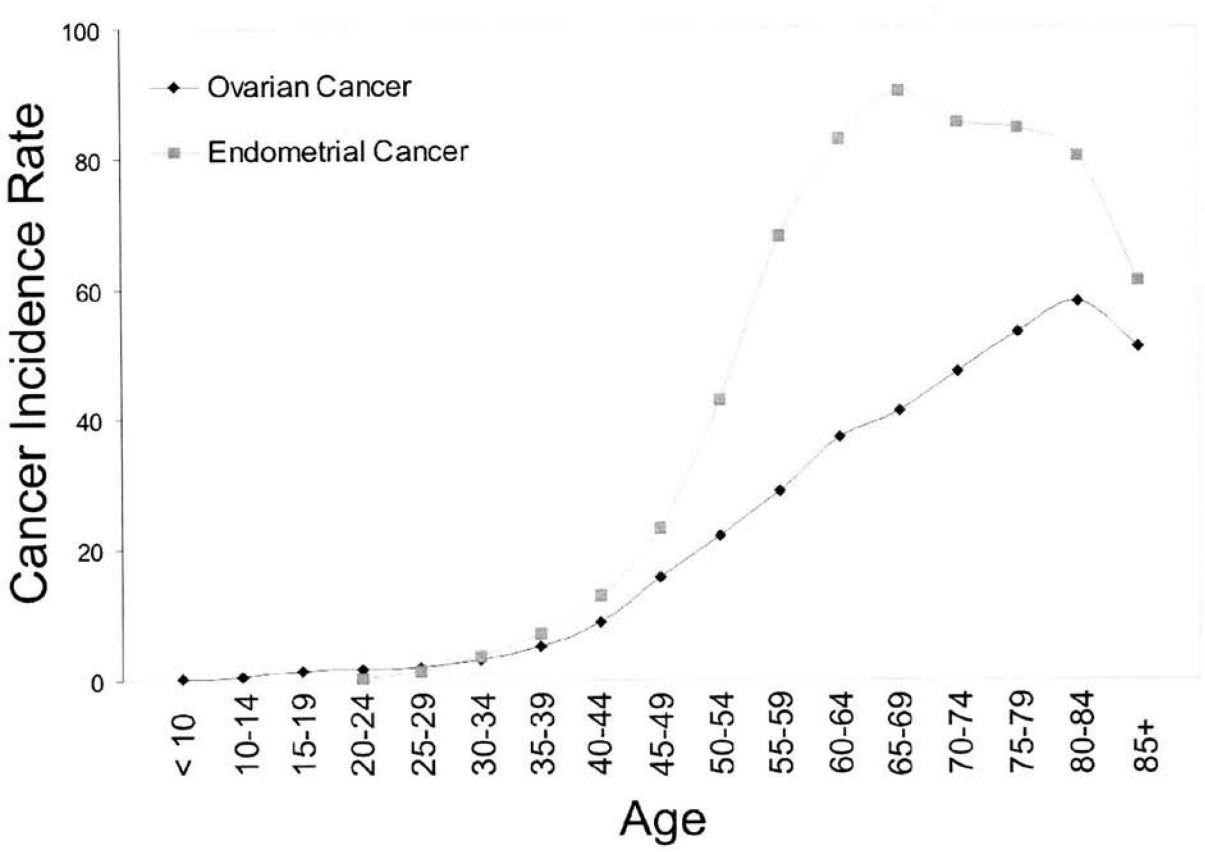

Figure 1.

Age-Specific Incidence Rates of Endometrial and Ovarian Cancers[1].

[1]Age-Specific Cancer Incidence Rates are per 100,000 and are age-adjusted to the 2000 US Standard Population. Rates include all races and pertain to invasive cancers only. Adapted from Ries *et al.* [199] http://seer.cancer.gov/csr/1975_2005/.

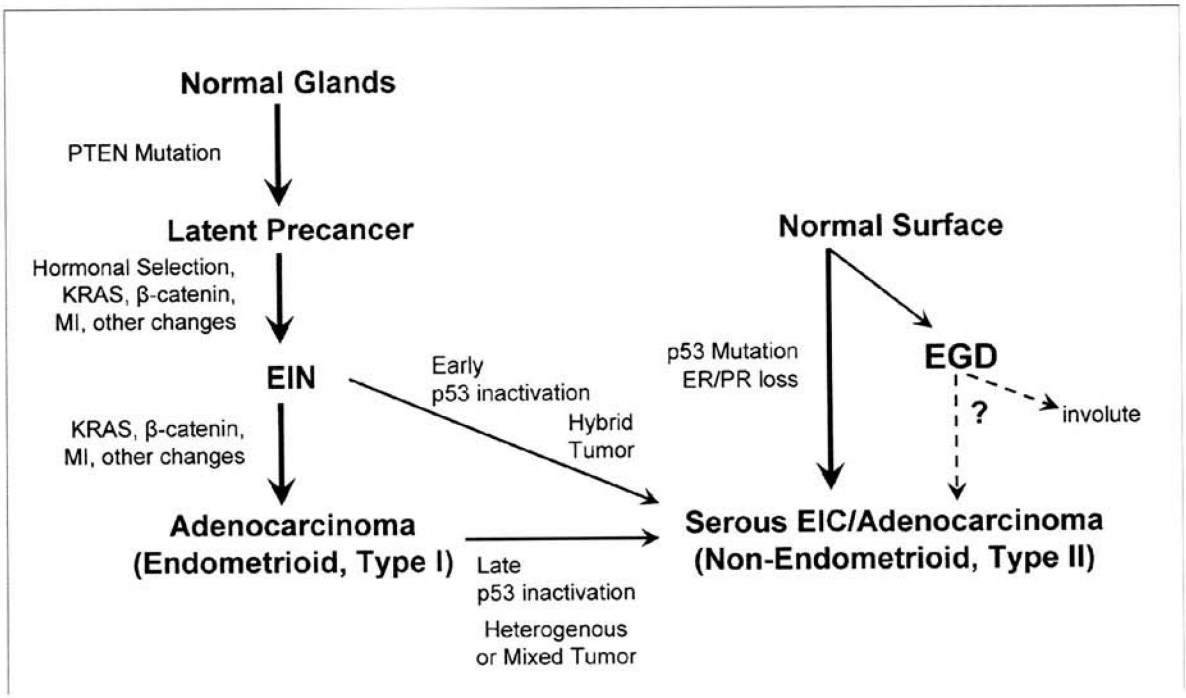

Figure 2. Multiple Pathways to Endometrial Carcinoma

Inactivation of PTEN occurs early in Type I endometrial carcinomas, prior to any detectable histologic change (“latent precancer”). Non-genetic hormonal selection factors, such as increased estrogen unopposed by progesterone, may modulate cancer risk through their actions on preclinical latent precencers, which may undergo involution or expansion with additional mutation. Further mutations, sometimes accelerated by a microsatellite instability phenotype (MI), define stepwise progression events to EIN and then adenocarcinoma. Serous (Type II) tumors are initially observed as short-lived preinvasive precursors designated as serous intraepithelial carcinoma (EIC). Endometrial glandular dysplasia (EGD) is a newly described lesion with p53 inactivation and a histology that is intermediate between normal and serous EIC. Progression and involution rates of EGO lesions over time are unknown and it remains to be determined how often EGD lesions are actual precursors of Type II cancers. Rarely, individual examples of Type I tumors may acquire an early or late p53 inactivation event, causing a hybrid or heterogeneous tumor, respectively [adapted from reference 43]

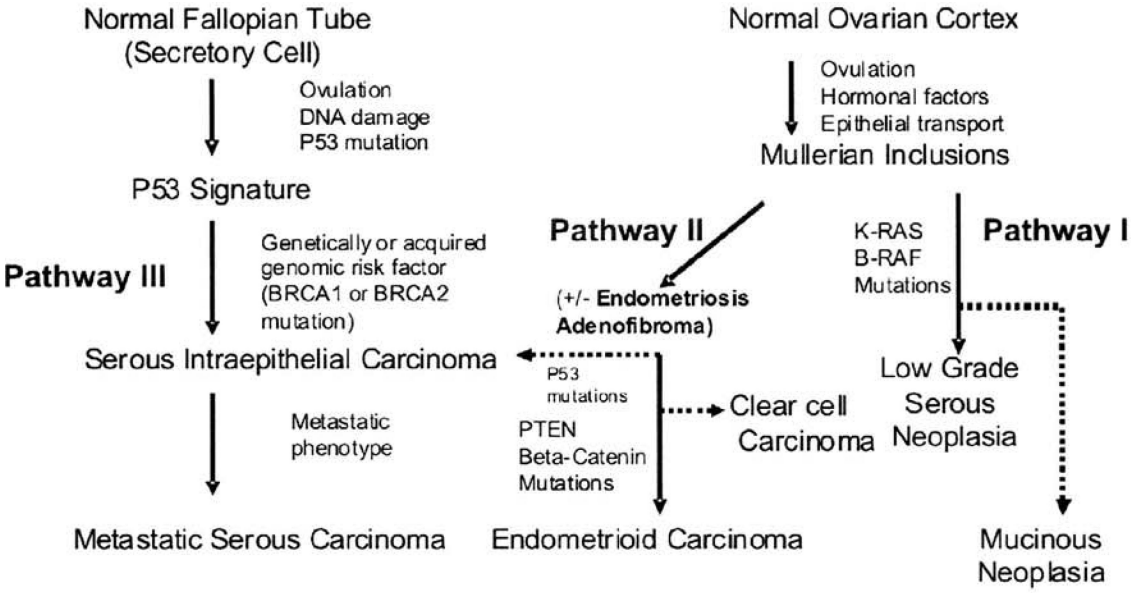

Figure 3. Relationship between Potential Precursor Lesions and Histologic Types of Ovarian Cancer

Three pathways for ovarian cancer are proposed: **Pathway 1** begins in the ovary in a majority of cases within Mullerian inclusion cysts (MICs). MICs may form when the ovarian surface or other epithelium (such as salpingeal) becomes entrapped after ovulation or by surface adhesion. MICs have been the classic explanation for the origin of benign serous and mucinous cystadenomas, some of which may progress through borderline counterparts, serous borderline or mucinous borderline, into carcinomas. Pathway I may apply to some low grade invasive serous carcinomas. **Pathway II** describes the origin of endometrioid and clear cell carcinoma from endometriosis derived from transpo1t and implantation of endometrial cells from the uterus. Counterparts of each type may occur in the uterine lining. **Pathway III** involves the origin of metastatic (high grade) serous carcinomas and is best characterized in the distal fallopian tube [adapted from 128].

Table 1

Age-Adjusted Incidence Rates[1] for Endometrial and Ovarian Cancers in Different Regions of the World.

Region	Endometrium	Ovary
World	6.5	6.6
More developed countries	13.6	10.2
Less developed countries	3	5
Eastern Africa	3.2	5.8
Middle Africa	2.5	3.3
Northern Africa	2.4	2.6
Southern Africa	3.5	52
Western Africa	2.2	4.6
Caribbean	8.8	4.3
Central America	4.5	7.2
South America	6.7	7.7
Northern America	22	10.7
Eastern Asia	2.5	3.7
South-Eastern Asia	4.2	7.2
South Central Asia	2.3	5.3
Western Asia	5.8	5.3
Eastern Europe	11.8	10.2
Northern Europe	12.2	13.3
Southern Europe	11.8	9.7
Western Europe	12.5	11.3
Australia/New Zealand	10.6	9.4
Melanesia	6.7	6.6
Micronesia	7.4	6
Polynesia	11.8	7.7

[1] Age-Adjusted Incidence Rates are per 100,000 and are adjusted to the World Standard. Incidence rates are highly correlated (Pearson correlation = 0.81, $p<0.001$). Data from Ferlay *et al.* [161], IARC website (http://www-dep.iarc.fr/).

Table 2

Risk factors for Endometrial, Breast, and Ovarian Cancers[1]

Factor	Endometrium	Ovary	Comment	References
Menstrual, reproductive, and medical events				
Menarche	↓	↓	Late age	[162-164]
Cycle Length	↑	↑	Short or irregular cycles	[162, 164-167]
Menopause	↑	↑	Late age	[2, 168]
Early Age at First Birth	↓	↓	Late last birth also decreases endometrial and ovarian cancer risk	[167, 169]
Parity	↓	↓		[167, 169]
Breastfeeding	↓	↓		[170-174]
Oral Contraceptives	↓	↓	Non-sequentials decrease endometrial cancer risk	[106, 175-178]
Ovulatory cycles	↑	↑		[5, 179, 180]
Menopausal Hormones	↑	↑	Unopposed important lo endometrial cancer risk	[181-186]
Body Mass Index	↑	↑		[15, 16, 187, 188]
PCOS	↑	↑		[17-19]
Genetic/ familial syndromes				
Cowden's Syndrome	↑	Ø		[24]
BRCA1,2	↑	↑		[21, 189]
HNPCC	↑	↑		[22, 23]
Other environmental factors				
Smoking	↓	↑	Ovarian cancer risk is restricted to mucinous histology	[35, 36, 190-193]
Talc use	?	↑		[37-40]
Tubal Ligation	↓	↓		[31-34, 194]
Intrauterine Device Use	↓	↓	Ovarian cancer association is possible	[27, 29, 30, 195, 196]

[1] A positive association is indicated by ↑, negative association by ↓, and no association as Ø. A '?' represents too little data to determine whether an association exists.

Table 3

Histopathologic Categories of Endometrial Cancer [adapted from references 197, 198].

Type	Histologic description	Comments
Endometrioid	Resemblance to benign endometrial epithelium. Composed of tubular glands, lined by stratified or pseudostratified columnar cells. Nuclear pleomorphism is often mild to moderate.	
Serous	Forms complex papillary fronds covered by stratified, highly atypical epithelial cells that often display marked nuclear pleomorphism, and numerous mitoses. Exfoliation of cells (“hobnail”) and psammoma body formation (calcium deposition on intracytoplasmic filaments of degenerating cells) may be observed.	Similar histology to that seen in the ovary. Typically behaves aggressively with tendency for myometrial invasion, extensive lymphatic invasion and early dissemination. This subtype is regarded as high-grade by definition
Clear Cell	Clear, glycogen-filled hobnail-like cells with highly pleomorphic nuclei. Cells often grow in tubular or papillary arrangements. However, unlike serous carcinoma, papillae often have hyalinized cores.	Generally presents as advanced stage and has a poor prognosis
Mucinous	Composed of endocervical-type columnar cells that contain mucin-rich cytoplasm.	Tumors are most often low grade. Mixed endometrioid and mucinous adenocarcinomas are relatively common.
Squamous	Patterns range from individual cell keratinization to the formation of large keratin masses.	Pure squamous neoplasms are rare however focal squamous areas are identified in a portion of endometrioid carcinomas.
Transitional Cell	Typically displays nested or papillary urothelial morphology including longitudinal nuclear grooves	Pure primary tumors are rare.
Carcinosarcoma	Display an admixture of carcinomatous and sarcomatous components. The epithelial component is usually high grade and can be of endometrioid (most common), serous, clear cell, mucinous, undifferentiated or squamous type. The sarcomatous component may resemble endometrial (homologous) or non-endometrial (heterologous) stroma.	Also known as Malignant Mesodermal (Mullerian) Mixed Tumor.
Undifferentiated	Lack a distinctive appearance therefore unable to classify into specific category of tumor. Often composed of diffuse sheets and nests that display extensive necrosis.	Associated with poor prognosis

Table 4

Histopathologic Categories of Epithelial Ovarian Cancer [adapted from reference 50].

Type	Histologic description	Comments
Serous	Low and high grade subtypes distinguished by nuclear cytology correspond to different clinicopathologic subsets. External surfaces may be covered with papillary fronds and papillae that may become fused and form slit-like spaces. Psammoma bodies are often seen.	
Endometrioid	Resembles endometrial epithelia. Exhibits distinctive tubular glands lined by a pseudostratified epithelium with little or no intracellular mucin.	Histologically identical to endometrial endometrioid carcinoma. Often seen in association with endometriosis Concomitant endometrial carcinoma present in one-quarter of cases.
Mucinous	Epithelial lining of glands and cysts may be intestinal (goblet cells scattered among mucin-free cells) or endocervical/ mullerian type (mucin-filled, columnar cells with basal nuclei). Many or all of the cells contain abundant intracytoplasmic mucin.	Many intestinal type tumors now recognized as metastatic from appendix or large bowel.
Clear Cell	Cells are hobnail-like with glycogen-rich, clear cytoplasm and highly pleomorphic nuclei. Multiple papillae often encountered.	Histologically identical to clear cell carcinoma of the endometrium.
Squamous	Cell keratinization is common.	Pure squamous cell neoplasms are rare. Squamous elements are often seen in endometrioid tumors
Transitional Cell	Characterized by nests and columns of ‘transitional type’ epithelial cells that resemble the lining of the urinary bladder.	Includes malignant Brenner tumors and Transitional Cell Carcinoma.
Malignant Mesodermal (Mullerian) Mixed Tumors	Tumors contain both epithelial and mesenchymal elements. The epithelial component most often resembles endometrioid or serous carcinoma, but occasionally mucinous, squamous or clear cell elements are observed.	Most tumors are identical to those that are more frequently encountered in the endometrium.
Undifferentiated	Lack a distinct appearance and may exhibit a variety of growth patterns such as solid masses and irregular nests of epithelial cells separated by stroma that may be desmoplastic. Psammoma bodies, glands, papillae and mucinous pools may be present.	