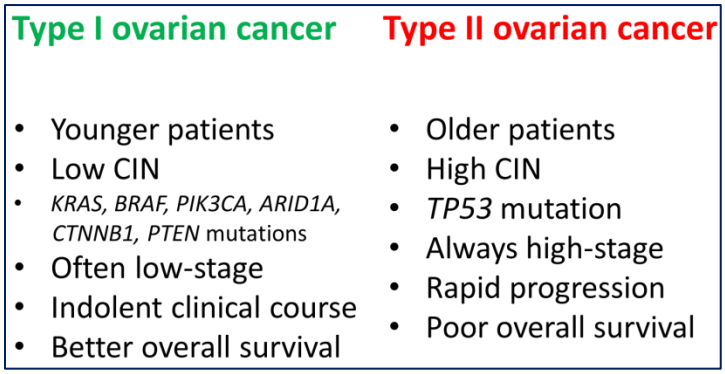
The pathogenesis and origin of ovarian cancer

Ie-Ming Shih, Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

Primary ovarian carcinoma is a heterogeneous group of diseases and each subtype is characterized by distinct clinical, histologic, and molecular features. Ovarian cancers can be broadly subdivided into Type I and Type II tumors. This classification is not a histologic one, but describes tumorigenic pathways based on clinically correlated molecular data. Type I tumors include low-grade serous, low-grade endometrioid, clear cell and mucinous carcinoma and typically present as a mass confined to the ovary and have a relatively good outcome. Type II tumors include high-grade serous carcinoma, high-grade endometrioid carcinoma, carcinosarcomas and undifferentiated carcinomas. These tumors are highly aggressive and typically present as advanced stage disease with poor outcomes. Two of the recent research spotlights in ovarian cancer field are: **1)** elucidation of the origins of high-grade serous carcinoma, and **2)** the revelation of genome-wide molecular landscapes of different histological subtypes of ovarian cancer. Mounting evidence has provided new evidence to argue that ovarian high-grade serous carcinoma may not originally develop from ovary. Rather, many of them are derived from fallopian tube epithelium then involve ovarian tissues secondarily. Similarly, it has been recognized that both ovarian clear cell carcinoma and endometrioid carcinoma develop from ovarian endometriomas which represent ectopic endometrial tissues. Accordingly, the only true primary ovarian neoplasms are gonadal stromal tumors and germ cell tumors, analogous to tumors in the testis. Recent efforts in comprehensive analysis of genomic changes have revealed the landscapes of many subtypes of ovarian cancer. It comes with no surprise that different types of ovarian cancer have unique landscapes that have profound implications on their pathogenesis and provide blue prints for future development of new strategies in early detection, prevention and targeted therapy. Both topics as outlined above will be discussed in the lecture and their highlights are briefly summarized in this abstract.



1. Origin of “ovarian” cancer

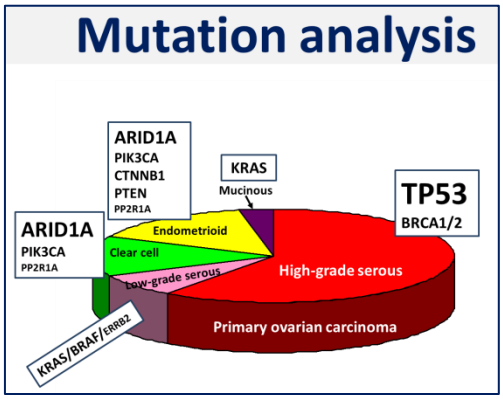
Recently, a new paradigm has emerged for the carcinogenesis of ovarian cancer. It was classically hypothesized that ovarian cancer was derived from the ovarian surface epithelium exposed to repeated trauma and repair as a result of cyclic ovulation. However, evidence for this theory is generally lacking and a precursor lesion within the ovary has rarely been confirmed. In 2001, Piek et al described dysplastic lesions similar to high-grade serous carcinoma exclusively in the fallopian tube, and not in the ovary, of women with a genetic predisposition to epithelial ovarian carcinoma undergoing prophylactic bilateral salpingo-oophorectomy (BSO). This launched the characterization of “serous tubal intraepithelial carcinoma (STIC),” a tubal lesion that is thought to represent the precursor lesion of high-

grade serous carcinoma. The evidence is accumulating and includes 1) STICs can be frequently found in high-grade serous carcinomas and also in some percentages of fallopian tubes that are removed prophylactically; 2) SITCs were only associated with high-grade serous carcinoma but not other types of gynecologic malignancies; 3) identical TP53 mutations in both STIC and high-grade serous carcinoma from the same patients in the majority of cases, indicating their clonal relationship; 4) STICs contain relatively shorter telomeres and fewer centrosome number abnormality than the concurrent high-grade serous carcinoma, a finding supporting that STIC is likely a precursor rather than tumor dissemination from carcinoma. In light of new evidence which strongly suggests that ovarian high-grade serous carcinoma begins outside the ovary, the implications for detection and management are substantial and they are summarized in the following Table.

Ovarian origin	Tubal origin	Rationale
Detection of stage I HGSC as the major focus	Efforts on detecting low-volume HGSC rather than on detecting stage I Dx	"Ovarian" cancer is by definition is not stage I disease because the carcinoma develops in FT then disseminate to ovarian and peritoneal tissue/omentum.
For high-risk patients, prophylactic RRSO is performed	Prophylactic salpingectomy should be performed in premenopausal women	Sparing ovaries can preserve fertility and hormonal function in premenopausal women.
TAH is performed for benign uterine Dx	TAH + bilateral salpingectomy with sparing of the ovaries	This may lead to a decrease of risk in developing HGSC because FT is the origin of HGSC.
Tubal ligation for sterilization	Salpingectomy is recommended	Removal of the entire fallopian tube eliminates tubal epithelial cells which may develop into HGSC.
In research, OSE (cultures) as normal control	Fallopian tube epithelium as a more appropriate control	This is because FT epithelium is the origin of STIC and HGSC. In contrast, OSE is mesothelial rather than Mullerian origin.
In pathology practice, FT is examined representatively	FT should be completely submitted and thoroughly examined	Examination of the entire FT may detect precursor and in situ lesion of HGSC, such as STIC.

2. The genomic landscape of ovarian cancer

With the advent of whole genome sequencing, each subtype of epithelial ovarian carcinoma now has its own molecular map consisting of specific genetic alterations by which each can be identified. Genome-wide analyses including whole exome sequencing and DNA copy number changes have been performed in several types of ovarian epithelial tumors including ovarian high-grade serous carcinoma, ovarian low-grade serous carcinoma, and ovarian clear cell carcinoma. Candidate gene approaches have also been reported in those tumors and ovarian endometrioid



carcinoma and mucinous carcinoma. The somatic mutation signatures in each type of ovarian carcinoma are illustrated in this figure.

High-grade serous carcinoma: *TP53* mutation is the major molecular genetic change of high-grade serous carcinoma (HGSC). The Cancer Genome Atlas (TCGA) ovarian cancer data demonstrate that approximately 96% of HGSCs harbor *TP53* mutations. Recently, a group of gynecologic pathologists re-analyze those few cases with sequence wild-type *TP53* find that most of the tumors with wild-type TP53 are either misdiagnosed or are cases with mixed features, a result indicating that TP53 mutation occurs in virtually all HGSCs. This finding also suggests that a pelvic carcinoma suspious for HGSC is unlikely a true HGSC if it has wild-type TP53. *BRCA* represents another important gene as 25% of women with HGSC have either a somatic or germline mutation or hypermethylation of the *BRCA* promoter region. Rather than intragenic mutations involving encoded proteins, chromosome instability with allelic imbalance and DNA copy number changes is characteristic of HGSC. The TCGA also identified a large number of copy number alterations targeting several cancer-associated genes including *NOTCH3, CCNE1, MYC, TERT* and *NF1*. Among amplified genes, NOTCH3 amplification and pathway activation play a causal role in developing chemoresistance and tumor recurrence in HGSC. A research group has measure the chromosomal disruption index by calculating the extent and levels of DNA copy number changes and reported that patients with optimal debulking and a low chromosomal disruption index have a significantly better overall survival than those with a higher index. Though such molecular data is promising, it has not yet matured to affect the clinical outcome for women with HGSC.

Low-grade serous carcinoma: Genome-wide analysis of the whole exome sequence and DNA copy number changes of low-grade serous carcinoma (LGSC) have been performed. The most interesting finding is that LGSC, like its precursor lesion, serous borderline tumor, frequently harbors KRAS and BRAF mutations and in contrary to high-grade serous carcinoma, this type of tumors usually lacks *TP53* mutations and remains chromosomally stable. The MAPK pathway plays an important role in the pathogenesis of LGSC. Specifically, greater than 60% of these tumors demonstrate mutations in *KRAS, BRAF* or *ERBB2* genes which result in activation of the MAPK pathway. Farley and colleagues demonstrated promising results for the MEK1/2 inhibitor, Selumetinib, to downregulate MAPK activation in women with recurrent LGSC in a phase 2 trial. Of the 52 women enrolled in the trial, 15% had an objective response and 65% had stable disease. Though there were only a small number of patients enrolled in this trial and data for overall survival requires larger numbers and longer follow-up time, the positive results demonstrate the importance of understanding a tumor's molecular landscape for exploitation by targeted therapy.

Clear cell carcinoma: Genome-wide analysis of sequence mutations has revealed the molecular genetic landscape of ovarian clear cell carcinoma (CCC). The most frequently mutated gene is *ARID1A*, which is mutated in approximately 50% of CCCs. Mutations are largely frameshift and nonsense, leading to lost expression. Functional studies have provided new evidence to support that ARID1A is a bona fide tumor suppressor that collaborates with p53 to regulate CDKN1A and SMAD3 transcription and tumor growth in gynecologic cancers. Loss of ARID1A expression, presumably due to mutations, appears as an early event in tumor progression from an ovarian endometriotic cyst to a CCC.

Endometrioid carcinoma: There are several genetic mutations associated with ovarian endometrioid carcinoma (EC) such as *ARID1A, CTNNB1* and *PTEN.* In addition, EC is also characterized by microsatellite instability. Such mutations are also commonly found in uterine EC. Similar to CCC, ARID1A mutation has been found in up to 40% of ovarian EC. Ayhan and colleagues reported an interesting finding using ARID1A immunohistochemistry on 47 carcinomas. ARID1A loss was concomitant in 31 tumor cells and contiguous endometriotic cyst epithelial cells, however ARID1A was retained in cells not adjoining tumor. Furthermore, 16 carcinomas with retention of ARID1A expression also demonstrated ARID1A expression in epithelial cells. As a result, the expression patterns of this tumor suppressor gene provide a strong argument for its role in ovarian EC development. The *CTNNB1* gene encodes β-catenin which is most often up-regulated as a result of activating mutations of *CTNNB1* which is not found in other types of ovarian carcinoma. β-catenin plays an important role in the Wnt signaling pathway which is dysregulated in 16-38% of EC. Mutations in *PTEN* are also uncommonly found in other types of ovarian carcinoma, but are described in 14-20% of EC. A unique loss of heterozygosity mutation at the 10q23 locus has been identified both in EC and adjacent benign endometriotic cyst cells. Microsatellite instability is present in 13-20% of EC and caused by the downregulation of mismatch repair genes such as MLH1 and MSH2 either by sequence mutations or by promoter hypermethylation.

Mucinous carcinoma: The most common mutations in mucinous ovarian carcinoma (MOC) are activating *KRAS* mutations and have been detected in 85% of these tumors. Identical mutations have been identified in cystadenomas with adjacent carcinoma, suggesting a role for *KRAS* in early tumor development. MOCs also express genes associated with mucin production, the most prevalent of which is *galectin 4* (LGALS4). LGALS4 is an intestinal-type cell adhesion molecule found in intestinal carcinomas and is also upregulated in MOCs compared to other types of ovarian carcinomas.