WARNING

Medical information is continuously renewed day by day. During reading this book, it should be kept in mind that some changes may be necessary in the treatment and drug administration protocols in the light of the evidence coming from the current literature. Always, safety standards should be applied on management of patients. It is advised for the readers to check once more the information of the drugs related to the product info, dosage and administration forms and contraindications before administering the drug to the patients. Publishers and the editors are not responsible for any medical damage to the patients or the equipments.

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"An innovative presentation of great topics! It is the "must have" for everyone interested in Gynaecologic Oncology! It covers all fields of Gynaecological Oncology - from basic articles to controversial discussions on cutting edge subjects. Includes famous Gynaecologic Oncologists writing about their field of speciality – an absolute must read!"

Dr. Michaela Bossart, Germany

"The textbook is an easy to read and very complete guide on Gynecologic Oncology. The quality of authors is awesome and the contents concise and practical. It's a great introduction and good general view of all aspects of the subspecialty; this without a doubt should be the reference for young trainees. Congratulations on a great job."

Dr. Ignacio Zapardiel, Spain

"The 1st edition of the Textbook contains comprehensive coverage of the huge field of Gynaecological Oncology. On the one hand it provides a basic knowledge on topics of interest for trainees, on the other hand, specialists can find up to date information on surgery, radiotherapy, chemotherapy and imaging specialties. Every single topic provides insightful information and areas for discussion. It gives a wonderful overview of the pros and cons and provides a platform for discussion in the most discussion provoking areas of our subject."

Dr. Rene Laky, Austria

"This edition covers the most interesting topics of Gynecologic Oncology and will be incredibly useful for trainees and young doctors. The book includes topics of gynaecancer and pregnancy that is also very important and useful for the clinical practice of each OBGYN doctor. It is great to have a book that introduces all new technologies and management in Gynaecological Oncology."

Dr. Suzanna Babloyan, Armenia

"A thoroughly enjoyable read! It is a great first edition, extremely comprehensive covering several complex topics and areas of interest for trainees. It helped me personally to improve my understanding in a number of interesting areas and it is a good reference book. I congratulate the editors, the authors and ESGO on this massive effort!"

Dr. Ranjit Manchanda, UK

"Excellent! Covered several different topics and answered many pending questions. The combination of the enthusiasm of ENYGO's authors along with the experience of the senior authors makes the book unique. Can be read by the young residents of gynecology as well as by the senior gyn oncologists - both will find topics of their interest. Simply mesmerizing!"

Dr. Dimitrios Haidopoulos, Greece

"The first edition is a very interesting book on gynecologic oncology, extremely clear on different topics and easy to consult also for trainees. Each chapter has been written by the experts in gynecologic oncology, very useful in clinical practice. Great references. Congratulate the editors and authors for their efforts."

Dr. Michele Peiretti, Italy

"Exceptional work which is due to its rapidness of the writing and up-to-date editing as an journal article whilst maintaining the comprehensiveness of a textbook. The author list presents all the most famous current onco gynaecologists which makes the texts scientifically outstanding."

Dr. Michael Halaska, Czech Republic

"In itself the idea of creating this book is an ambitious, timely and grandiose one. Many thanks to the Editors and ESGO/ENYGO for the ability to realize this idea. Authorship of the main chapters belongs to the most competent and qualified specialists in this area. The book is very useful not only for beginners, but experienced doctors. It is very convenient to have such a Clear Guide with the final recommendations in diagnostics and treatment of the reproductive tract malignances."

Dr. Elena Ulrikh, Russia

"The textbook is easy-to-read and understand. It should be on the shelf of every gynaecologic oncologist's office. Makes a difference on an every day basis. The authors' tremendous amount of knowledge of the area is quite evident. A must for all gynecologic oncologist's..."

Dr. Karina Dahl Steffensen, Denmark

"The textbook has been written in easy and smart style. All-round contents of contemporary gynecologic oncology (including even history!) and breast cancer enables any interested doctor or tutor to find useful information easily. It makes this textbook a table-book for onco trainees, young specialists and experienced doctors. Of course, for me too!"

Looking forward to receiving the second edition!

Dr. Gauhar Dunenova, Kazakhstan

"This is a very good book which aggregates most of the techniques, knowledge and expertise in Gynaecologic Oncology in a very accurate and interesting way. Both trainees and specialist benefit from reading it."

Dr. Filipe Martins, Portugal
Preface to the Third Edition

The European Society of Gynaecological Oncology is proud to present to you the third edition of its textbook.

This textbook is one of our most ambitious and successful educational projects. It is built on the unique ESGO network of experts, who have voluntarily compiled topics in which they are the key opinion leaders.

Each edition reflected recent developments in gynaecologic oncology but gradually it has expanded into other specialities and that makes the book truly multidisciplinary.

The textbook does not represent for ESGO an isolated initiative; it is part of a logical and mutually complementary mosaic, together with many other educational projects such as web portal e-Academy, traditional bi-annual congresses, a new format of State-of-the-Art meetings in the odd years when the congress is not held, dozens of ESGO-endorsed sessions, videos of surgical procedures, teaching DVDs, etc.

On behalf of the ESGO Council, I would like to extend my gratitude for and appreciation of all the contributing authors and their co-workers. A special credit goes to two men behind the textbook, Dr. Murat Gultekin, who initiated and run the project, and Dr. Nicholas Reed, who carefully revised and refined the majority of the chapters.

I can proudly encourage you to commence your reading!

David Cibula
ESGO President
Dear All

Gynaecologic Oncology, our lovely profession, take more and more acceptance since its first establishment. It requires a multidisciplinary team to provide the diagnosis, treatment and postoperative care of the cancer patients. Therefore, a didactic training program is necessary for the management of patients with gynaecologic cancers. Unfortunately, despite the fact that most of the gynaecologic cancers seen in undeveloped or developing countries, official gynecologic oncology training programmes are approved in only a few number of well developed countries.

Our main intend to edit such a book was to be contribute to the gynaecologic oncologic training; especially in countries where such an official training is not available. Our goal was to provide a comprehensive and practical book to guide gynaecologic oncology workers. With this purpose, “Textbook of Gynaecologic Oncology” was written to provide a concise update of current clinical gynaecologic oncology. As editors, we tried to include all the subjects of gynaecologic cancers from preinvasive diseases to metastatic diseases. Surgical and medical treatments of all gynaecologic oncologic diseases are summarized by the authors.

We also tried to include the new surgical and medical developments in gynaecologic oncology. There are discussions about the most debate areas of gynaecologic oncology and review of multinational trials. Also, future aspects of gynaecologic oncology and recent advances are reviewed.

I would like to thank to ESGO council and Prof. David Cibula, President of ESGO, for their endless support for the preparation of this book.

Such a comprehensive textbook is not possible without the help of our colleagues. The authors of this book are chosen all around the world and are very famous in their topics. As you will see from the list of authors, this book almost include all the living pioneers and famous gynaecologic oncologists. Many thanks are due to all the authors who have contributed to this book and also editorial staff of Güneş Publishing. We would like to also specially thank to our co-editors. Without their tireless efforts, this book has never come to reality.

The knowledge and love increase with sharing
May wisdom and love reign in the light of intelligence

Ali Ayhan - Murat Gultekin - Polat Dursun
Preface to the Third Edition

It is a remarkable achievement that within 7 years this book has run to a third edition and the editorial team working with ESGO, ENYGO and the Turkish Society of Gynaecologic Oncology must be congratulated for producing such a remarkable volume. So many of the world’s leading experts have voluntarily contributed state-of-the-art chapters in a remarkable turnaround time. As one of the editors I have read just about every chapter and can vouch for the clinical excellence and up-to-date status. Although hard work at times and demanding when a batch of 10 chapters was sent in, it has been a pleasure to read and review these. It is a credit to all the societies involved and is fantastic asset for trainees in all disciplines of gynaecological oncology. I think it will also be a wonderful asset for established specialists who will find its state-of-the-art references an invaluable resource. If the reader feels that there are areas of overlap with some of the chapters, this is because we had tried to get as many viewpoints as possible. Medicine is not black and white and in many situations there are varying shades of grey and opinions. We also try to reflect international practice with expert contributors from the Americas, Central Europe, the Middle East, South Asia, the Far East and Australasia. Of course the world is shrinking place with modern travel and we are a far more integrated Society, but there are cultural and ethnic diversities which are reflected in medical practice. We also recognise that resources vary internationally and that not every Centre has access to robotic surgery, PET/CT scanning all the latest targeted chemotherapy agents even though they may aspire to them. However what they do have is enthusiastic and dedicated surgeons, oncologists, pathologists, radiologists and nurses.

In this modern age where so much information and learning is gained digitally through the Web, it is remarkable to have a physical resource which is so up-to-date and supportive. Once again I must congratulate Murat Gultekin and Polat Dursun for the never-ending enthusiasm support and professionalism in persuading busy gynaecological Cancer specialists all around the world to either update their chapters or write new chapters. I would also like to pay tribute to Professor Ali Ayhan without whose original stimulus, this project would never have got off the ground. It has been a great honour and pleasure to be associated with this third addition and we look forward to future additions although whether these are conventional book forms ordered DVD discs. Finally I would like to acknowledge a wonderful work of the production team, especially Irem Kucukyildiz and Mujdegul Karaca without whose enthusiasm and support this would never have been produced.

Nicholas Reed, Glasgow UK
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The Non-Ovarian Origin and Pathogenesis of Ovarian Carcinomas: Update on the Pathological and Molecular Clues

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Introduction

Ovarian cancer remains the most lethal gynaecological malignancy, despite the significant advances over last decades in imaging technologies, surgical techniques, chemotherapeutic regimens and delivery strategies. Classically, ovarian cancer has been classified based on histological types and treated as a “single” uniform disease. On one hand, the heterogeneity of primary ovarian tumors has been well accepted, and includes substantially epithelial, sex-cord stromal, and germ cell tumors that parallel the distinctive cellular compartments of such a unique organ. On the other hand, both sex-cord stromal and germ cell tumors undoubtedly originate from the ovary itself, analogously to the testis (the male gonad), whereas the origin of epithelial tumors still remains by and large shrouded in darkness. The more we learn about the earliest histopathological features, molecular alterations and natural history of ovarian cancers, the more we have been questioning the historical terminology and classification.

The genuine purpose of any tumor classification is to make the terminology consistent and to standardize the criteria used in scientific investigations and by doctors, in order to generate most advantageous descriptors for the patients, to compare studies, and finally to better guide management, even when the therapeutic options are few. Tumors should therefore be sorted out with such a discerning formula to create a firm framework into which individual neoplasms that share specific factors, such as derivation (cell or organ of origin), histology, clinical behavior and management, fit in, forming the basis for integrity between clinicians, pathologists, and researchers. Determining the appropriate management based on the experience of well-characterized prior group of patients allows universal comparison thus transmission of evidence-based scientific know-how without ambiguity. The most commonly used staging system for malignant tumors is the TNM, elaborated and maintained by the collaboration of the AJCC (American Joint Committee on Cancer) and the UICC (Union for International Cancer Control). The TNM staging system describes the spread of tumor for each primary location based on the size and extent of the primary tumor (T), regional lymph nodes involvement (N) and presence of distant metastases (M) and is traditionally solely anatomic, but in recent years it is supplemented by designated non-anatomic prognostic factors. Notably, ovarian, fallopian tube and peritoneal tumors are described by the same staging system, since the ovarian and tubal tumors usually associate with a diffuse peritoneal dissemination.

Apart from the intratumoral heterogeneity, which occurs in any malignant neoplasm, the heterogeneity between different epithelial ovarian malignancies renders them a “group of diseases”, each of which should be clustered differently due to relevant differences in both morphology and clinical behavior, even if the origin were the same. On the basis of recent findings, the new understanding of ovarian epithelial carcinogenesis, laying the foundations on the cell of origin, the putative precursor lesions and molecular genetic alterations, compels us to reevaluate all the previous theories and to reconsider even the name. Therefore, in this chapter, we will trace the controversies in ovarian cancer field necessitating a prompt reevaluation and the misleading, even distorting facts that led the scientists unsighted for many years. Later we will touch upon the improved and updated model of epithelial carcinogenesis that divides ovarian cancer into two broad categories based on clinicopathological and molecular genetic features.

In our review we will focus on epithelial ovarian tumors (EOTs) and present the most recent experimental findings, the latest pathogenetic theories and our personal interpretations. First of all, what needs to be acknowledged is the heterogeneity and the difference of origin among the so-called “ovarian epithelial” tumors.

The Multiformity Of Epithelial Ovarian Tumors

Over forty years ago the World Health Organization (WHO) proposed the first classification of ovarian tumors, distinguishing EOTs in different histotypes,
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The main histotypes of EOC are further subclassified based on the degree of differentiation. The FIGO grading system has been recommended for both ovarian endometrioid and seromucinous carcinomas in the International Collaboration on Cancer Reporting data. For serous carcinoma, lately, it has advocated a two-degree system, replacing a three-degree system, that favours low-grade and high-grade not only for simplicity and reproducibility but also grounded on distinct molecular pathogenesis. Therefore, serous carcinoma has been dichotomized into low-grade and high-grade by the 2014 WHO classification. Though based on current terminology they appear as two morphological spectra of the same tumor, it should be stressed that they represent two different tumor types (3-5). Notably, both the histological subtypes and degree of differentiation correlate with clinical behavior of EOC.

**The Ovarian Surface Epithelium Origin: The Unifying Traditional Theory**

The female pelvic tumors manifest usually as a primary ovarian mass with various involvement of the peritoneum, as a consequence, it has been assumed that they primarily originate from the ovary, though EOCs show indubitable morphological resemblance to specific tissues not normally present in the ovary. In fact, the ovary is composed mainly of germ and stromal cells and virtually

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**Figure 1. Schematic representation of the ovarian surface epithelium hypothesis for the origin of epithelial ovarian cancers.**

Abbreviations: OSE, ovarian surface epithelium; CIC, cortical inclusion cysts; SC, serous cyst; MC, mucinous cyst; EC, endometriotic cyst; EOC, epithelial ovarian cancer; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; SMC, seromucinous carcinoma; EMC, endometrioid carcinoma; CCC, clear cell carcinoma.
no real epithelial cells, so that EOCs traditionally are thought to originate from the so called ovarian surface epithelium (OSE) or its invaginations into the ovarian cortex, named cortical inclusion cysts (CICs) (6, 7). The OSE is an innocent monolayered modified mesothelium that lines the ovary, with an uncommitted morphology and differentiation. Therefore, to reconcile the unspecialized morphology of OSE with the morphological heterogeneity of EOTs, the OSE was believed to carry the potential of differentiating in different epithelial directions, as previously mentioned, recapitulating the divergent specialization similar to those shown by the Müllerian duct epithelium during normal embryonal development (Figure 1). Coherently, CICs show variable morphological characteristics and immunophenotypes (8). Ultimately, a common histogenesis from a single cell type was a convenient and readily understood concept to group the majority of epithelial neoplasms occurring within the ovary. In this conventional view of ovarian carcinogenesis the “incessant ovulation” theory proposed by Fathalla indicates the cyclic ovulation and the repeated trauma and repair processes as the cause of DNA damage and consequent neoplastic transformation of the OSE (9).

The Controversies: Through A Renewed Manifold Theory

This theory has endured for over fifty decades in spite of numerous inconsistencies. First, as mentioned above, the common morphological features of EOTs do not mimic in anyway the normal appearance of OSE. In addition, Müllerian metaplasia derived from OSE should show, at least temporarily, intermediate hybrid phenotypes with contemporary expression of Müllerian and OSE markers, but this event is extremely rare. Second, OSE being phenotypically and ultrastructurally indistinguishable from mesothelium, its neoplastic transformation should theoretically look like mesothelioma and this is not true for EOCs. Third, the testis, the male gonad, similarly to the ovary is recovered by a modified mesothelium called the tunica albuginea, but only exceptionally develops epithelial tumors. Forth, only few reports have described putative precursor lesions, such as significant epithelial atypia, dysplasia or carcinoma in situ, involving the OSE or CICs (6, 10, 11). Fifth, the few molecular studies that have investigated OSE at a molecular level failed to identify differences in the expression of genes commonly deregulated in EOC. To our knowledge, few molecular alterations characteristic of EOC are documented in OSEs-CICs, such as the overexpression of p53 and TP53 mutations but just in few reports (12-15). Moreover, a recent molecular genetic analysis showed aneuploidy in CICs but not in the OSE (13) supporting the proposal that EOC indeed begins in these CICs rather than the OSE itself.

These inconsistencies have led investigators to propose the alternative origin from the “secondary Müllerian system” (16), which they defined as such “Müllerian epithelium-bounded structures found outside fallopian tubes, uterus, and cervix” (i.e. parovarian/paratubal cysts, endometriosis, endosalpingiosis, endomucinosis and rete ovarii) to account for the Müllerian phenotype expressed by most EOC. Also this occurrence is rather unlikely since Müllerian-type carcinomas developing outside the ovary, where the secondary Müllerian system is frequently found, are extremely uncommon.

The Tubal Origin of Serous Tumors

Serous carcinoma is the most frequent EOC. Currently, it is subclassified based upon its degree of differentiation in two main subtypes, high-grade serous carcinoma (HGSC) that alone accounts for more than 70% of the EOC, and low-grade serous carcinoma (LGSC) that represents around 5% of EOC. Based on biological, molecular and clinical-pathological evidences, they are two distinct entities, and the supposed progression between LGSC to HGSC appears more semantic than real in the majority of cases. However, there are growing evidences that both HGSC and LGSC may indeed derive from fallopian tube epithelium rather than OSE (Figure 2).

Serous Tubal Intraepithelial Carcinoma: The Watershed for High-Grade Serous Carcinoma

The OSE paradigm has started being revaluated, with regard to HGSC, since 2001 when Piek and al. described dysplastic lesions and occult HGSC in the fallopian tubal epithelium, but not in the ovary, in patients who had undergone prophylactic ovario-salpingectomy for germline mutations in BRCA1 and BRCA2 genes, that genetically predispose to HGSC. Subsequent studies have confirmed the presence of the tubal lesions, later called “serous tubal intraepithelial carcinoma” (STIC). Additional studies in which fallopian tubes were carefully examined by SEE-FIM protocol (i.e. sectioning and extensively examining the fimbriated end) have revealed that STICs and early invasive tubal carcinomas occur not only in women with a HGSC genetic predisposition, but also in 50-60% of women with sporadic HGSC (without either HGSC family history or known BRCA1-2 mutations) (17-25).

Further evidence supporting STICs as the precursors of HGSC has emerged by molecular studies, firstly the identification of identical TP53 mutations in STICs and concomitant ovarian HGSCs, indicating a clonal relationship between them (24, 26, 27). Further support of the link between STICs and HGSC was the demonstration that STICs and concomitant ovarian HGSCs, besides expressing alike p53, also co-express p16, FAS, Rsf-1, and cyclin E1 (28). We have also found
shortened telomeres, as occur in other precursor lesions, in the majority of STICs (29). Finally, we recently have reported concordant copy number of CCNE1, one of the most frequently amplified genes in HGSC, in STICs and concurrent HGSC and a more prevalent centrosome amplification in HGSC as compared to STIC; these findings further support latter as the HGSC precursor (30). Importantly, these lesions are generally detected in the fimbria. Therefore, it has been subsequently proposed that the implantation of malignant cells from the STIC to the ovary develops into a tumor mass that gives the impression that the tumor originated in the ovary (Figure 2) (31). In theory some STIC cell clusters detach from tubal mucosa, due to cell discohesiveness, and adhere to the disrupted OSE after ovulation (32), or onto the OSE and induce OSE displacement from the area underneath through a mechanism similar to that described for other peritoneal surfaces (33).

In hindsight, the logical assumption that the precursors of ovarian carcinoma would be found in the ovary delayed the identification of STIC, since the tubes were not carefully examined by pathologists (6, 7, 17). However, this STIC theory does not completely explain the origin of all HGSCs, so that incongruences still need to be pointed out. In fact, even the accurate SEE-FIM protocol does not allow to identify STIC lesion in a relevant percentage of HGSCs, at least 30%. In particular, HGSCs with a solid, pseudoendometrioid,
and transitional growth pattern (SET morphology) have a reduced prevalence of concurrent STICs, that implies the possibility of missing alternative HGSC precursors (34). One possible explanation is that small STICs can be missed despite complete sampling of the tubes. Another explanation is that indeed not all ovarian HGSCs arise from STICs, but some develop from the peritoneum, so-called “primary peritoneal carcinoma” or from the ovary. Yet possibility is that a minority of HGSCs develops from peritoneal endosalpingiosis or ovarian CICs. Although, endosalpingiosis and ovarian CICs instead to derive from metaplastic transformation of the peritoneal or ovarian mesothelium, could be derived from the fallopian tube epithelium, particularly of the fimbria, that implants onto the peritoneum or on the disrupted ovarian surface following ovulation (35). In fact, both endosalpingiosis and CICs frequently show morphological features and immunophenotype identical to fallopian tubal epithelium (36-39). Parenthetically, ovulation itself with the physiological mesothelial clearance may favor the adhesion of tubal fimbriae to the ovary, particularly in view of the close anatomical location. Moreover, the released follicular fluid during the ovulation has been shown to contain reactive oxygen species (free radicals) and high levels of sex hormones, which possibly induce changes in both the epithelial cells of fimbria and the local microenvironment, and so play a role in early ovarian carcinogenesis (40). This brings back and reconciles to Fathalla’s theory and is consistent with epidemiologic evidence linking decreased ovulations (either as a result of oral contraceptives usage or multiple pregnancies) with a decreased risk of ovarian cancer (41, 42). Therefore, some HGSCs may indeed develop from peritoneal endosalpingiosis or ovarian CICs (13) but these could very well be derived, at least some, from implanted fimbrial tubal epithelium (35). Parenthetically, gene expression studies show that HGSC resembles tubal epithelium rather than OSE, therefore gene expression profile associated with ovarian HGSC is consistent with a Müllerian (i.e. tubal) embryonic origin and not with mesothelial/urogenital/ovarian origin. Coherently, differently from OSE, immunohistochemically HGSC expresses Müllerian markers, as PAX8, but not mesothelial markers such as calretinin (35).

**Putative Precursors of Low-Grade Serous Carcinoma Into The Fallopian Tube**

LGSC is commonly associated with serous borderline tumors, and molecular evidences suggest that LGSC derives in a stepwise progression from a serous cystadenoma or serous adenofibroma through a serous borderline tumor to a noninvasive LGSC (i.e. micropapillary variant of serous borderline tumor) that finally becomes an invasive LGSC. Lately, some investigators have proposed that serous borderline tumors derive from fallopian tube epithelium, analogously to HGSC (37, 43, 44). In fact, a careful examination of fallopian tubes in women with serous borderline tumors has disclosed tubal proliferations in the form of PAX2-null secretory cell outgrowths or of the so-called “papillary tubal hyperplasia” (44, 45). This later lesion is characterized by small papillary formations of bland appearing tubal epithelium (with both secretory and ciliated cells) budding from the tubal epithelium, located in the tubal lumen, and often containing psammoma bodies. The authors have proposed that these detached papillae of tubal epithelium implant either on the ovary where they can develop into serous borderline tumor or on the pelvic or abdominal peritoneum to produce endosalpingiosis and implants (also in absence of borderline tumors). Furthermore, similarly to HGSCs, borderline tumors can originate from ovarian CICs, indeed deriving from tubal epithelium (Figure 2, right). As a matter of fact, CICs sometimes show papillary formations and they possibly may transform in borderline tumors (46). Both FTE and CICs are composed of a dual cell component, represented by secretory and ciliated cells, that is conserved in serous cystadenoma (37, 47). Furthermore, secretory cells increases progressively in serous borderline tumors, whereas LGSCs contain almost exclusively secretory cells, so that Li et al. proposed that LGSC pathogenetic pathway is due to a progressive clonal expansion of secretory cells and impaired maturation program (37).

**The Endometrial Origin of Ovarian Endometrioid, Clear Cell and Seromucinous Tumors**

Endometrioid and clear cell carcinomas are the most frequent types of EOC after serous carcinoma, accounting for approximately 15-20% of EOC in Western countries. Back in 1925 Sampson hypothesized that EOC arise from malignant transformation of endometriosis. Since that time, epidemiologic morphological and molecular studies have indicated endometriosis as the precursor of ovarian endometrioid, clear cell and, more recently, seromucinous tumors. Coherently, patients with endometriosis have about 3 to 10 times increased risk of developing ovarian endometrioid and clear cell carcinoma and, approximately 40% of ovarian endometrioid and 50-90% of clear cell carcinoma are associated with endometriosis (48-50). On the other hand, shared molecular genetic alterations revealing a clonal relationship between endometriosis and endometrioid and clear cell carcinoma, are supportive for the above hypothesis and will be described later in this chapter.

Endometriosis is a quite common chronic disorder affecting females in reproductive age, characterized by the growth of endometrial-type gland and stromal tissues outside of the uterine cavity. Its origin is still
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debated - either from retrograde menstruation-stem cell, coelomic metaplasia or Müllerian remnants. Although latter hypotheses are difficult to prove with experimental methods, there are accumulated evidences supporting the former; including but not limited to the following factors. First, endometriosis occurs exclusively in humans and primates, species that menstruate (51) and its increased risk is associated with increased menstrual exposure. Second, tubal ligation reduces the incidence of ovarian endometrioid and clear cell carcinoma (52). Molecularly, eutopic endometrium exhibits intrinsic molecular abnormalities similar to endometriosis in women with endometriosis, such as activation of the oncogenic Ras and Wnt pathways (53). Presumably, these changes favor endometrial tissue to survive, implant, and invade ovarian and peritoneal tissues.

Notably, even if endometriosis involves multifocally the pelvic cavity, the ovary represents, by far, the main site of cancer onset associated with endometriosis. As a consequence mainly endometrioma, i.e. ovarian endometriosis, represents the precursor of endometriosis-associated ovarian cancer (Figure 3). Coherently, both ovarian endometrioid and clear cell carcinomas associate specifically to endometrioma rather than endometriosis elsewhere. It is conceivable that, even if the endometriosis cyst fluid and microenvironment are characterized by inflammation and iron overload, that have been demonstrated to induce DNA damage and mutagenesis, driving malignant transformation, the latter may be accelerated and potentiated by ovarian microenvironment. Therefore, endometrioma–related EOTs would derive from endometrium through a long pathogenetic process. The endometrium cells settled into the ovary first would form an endometrioma or rarely an adenofibroma. The endometrioma epithelium exposed to high concentration of ferric iron, inflammation factors and sex hormones would progressively transform to become an atypical endometriosis, then a borderline tumor and

The Endometrioma Hypothesis

Figure 3. Schematic representation of the endometrioma hypothesis for the origin of endometriosis-related epithelial ovarian cancers. Abbreviations: EMAF, endometrioid adenofibroma; CCAF, clear cell adenofibroma; Atypical, atypical endometrioma; EMBT, endometrioid borderline tumor; CCBT, clear cell borderline tumor; EMC, endometrioid carcinoma; CCC, clear cell carcinoma.
finally an invasive carcinoma, specifically an endometrioid or clear cell carcinoma (Figure 3).

Endometrioid carcinomas of the ovary, as well as their uterine counterparts, harbor CTNNB1 mutations, mutations affecting the MAP kinase pathway, including BRAF and KRAS, and the PI3K/Akt pathway, including PIK3CA and PTEN, and microsatellite instability. In mice, endometriosis-like lesions carrying concurrent kras and pten mutations transform to invasive endometrioid carcinomas, suggesting that they represent early carcinogenic events. ARID1A somatic mutations occur in a large proportion of endometrium-related neoplasms, including 30 to 60% of ovarian endometrioid carcinomas, also in endometrioma, but not in eutopic endometrium (54). Moreover, ARID1A loss in both endometrioma and associated ovarian endometrioid carcinoma in most cases, indicate that ARID1A mutation is an early molecular event in the development of ovarian endometrioid carcinomas, that occurs before malignant transformation (55). Ovarian clear cell carcinomas harbor ARID1A mutations in up to 75% of cases and PIK3CA activating mutations in 20-40% of cases (56). Interestingly, same ARID1A and PIK3CA mutations are identified consistently in concurrent endometriosis when present in clear cell carcinoma (55, 57). Moreover, similar c-MET copy number appears in atypical endometriosis and adjacent clear cell carcinoma (50, 58, 59). Therefore, these data suggest that these molecular genetic aberrations likely represent early events during neoplastic transformation. Eventually, the molecular similarities of ovarian endometrioid and clear cell carcinoma are strong supportive evidences for their close relationship and origin from endometrioma.

A short paragraph is necessary to summarize seromucinous carcinomas. In fact, there are convincing evidences that these tumors are derived from endometriosis and must be included in the group of “endometrioma-related neoplasms”. Approximately one third of seromucinous tumors are associated with endometriosis, similarly to endometrioid and clear cell carcinomas, and show an immunoprofile resembling endometrioid and clear cell tumors (except that some are WT1 positive). In addition, mutant ARID1A in conjunction with loss of ARID1A expression is detected in one third of seromucinous tumors (60).

The common association of mucinous tumors with either teratoma or Brenner tumor suggests that they may take origin from both of these tumors. Interestingly, we recently proposed that, similarly to serous tumors, Brenner tumors originate from fallopian tubal epithelium at the tubal-mesothelial junction, where it is common to find transitional metaplasia (47). Based on our observations, these metaplastic foci, derived from the tubal epithelium at the tubo-mesothelial junction, would implant onto the ovary as Walthard nests and, under hormonal stimulation, would grow as a benign Brenner tumor. Successively, the progressive accumulation of molecular genetic aberrations would transform the benign Brenner tumor first to a borderline Brenner tumor, then rarely in a malignant Brenner tumor (61). In addition, Brenner tumors or their metaplastic precursors also may give rise to mucinous tumors (62). Then again, mucinous tumors may derive from endometrioma with mucinous metaplastic epithelium, through the mechanism described previously (i.e. endometrioma hypothesis, Figure 3).

Finally, the ovarian epithelial tumors may take the form of an undifferentiated carcinoma, this tumor does not show any Müllerian differentiation and based on the common association with low-grade endometrioid carcinoma and common molecular characteristics, at least a dual derivation can be inferred, through extreme dedifferentiation of either an endometrioid carcinoma or HGSC (63).

**Dualistic Pathogenetic Model of Epithelial Ovarian Tumors**

The heterogeneous nature of EOC has been united in a pathogenetic dualistic model that distinguishes two groups of EOC (type I and type II), based on different clinicopathologic and molecular genetic features (64). Type I tumors include low-grade serous, low-grade endometrioid, clear cell, seromucinous and mucinous carcinoma. They present as large masses, usually confined to one ovary (stage I), and have a rather good prognosis. They typically display a variety of somatic mutations that involve ARID1A, BRAF, CTNNB1, KRAS, PIK3CA, PPP2R1A, PTEN, RNF43 and hTERT, while only rarely TP53, and are usually genetically stable (58, 64-66). They are thought to develop in a stepwise fashion from benign lesions such as adenomas and endometriosis through borderline tumors. Constitutive activation of the PI3K/Akt and MAPK signaling pathways, due to somatic mutation of genes BRAF, ERBB2, KRAS, PIK3CA, and PTEN, seems to play a preeminent role in the carcinogenic process of type I tumors. On the other hand, type II tumors include HGSC, high-grade endometrioid carcinoma, carcinosarcomas (i.e. malignant mixed Müllerian tumors) and undifferentiated carcinomas,
which typically present in advanced stage (stages II-IV) and are highly aggressive. HGSC, the prototypical type II tumor, harbors TP53 mutations in more than 95% of cases, and BRCA suppression, either by mutation or via promoter methylation, in up to 40-50%, so that are genetically highly unstable (67). They only rarely display the mutations found in the type I tumors. Based on the fallopian tube hypothesis, type II tumors are established carcinomas from the beginning arising in the fimbria and capable of implanting on the ovary and other sites in the pelvic and abdominal cavities. The difference in the nature of the precursor lesions may explain why type I tumors remain confined to the ovary for a long periods and have an indolent course whereas type II tumors spread rapidly and are highly aggressive at their onset.

The updated model, based on recent molecular studies, underscores the heterogeneity of EOC, and emphasizes that type I and type II tumors are clinically two different groups of disease. It is important to point out to the reader that type I and type II tumor model refers to different “tumorigenic pathways” and that it has limited relation with diagnostic terminology, and to be honest, it is not perfect yet. As a matter of fact, recently we found that CCNE1 copy number gain characterizes clear cell carcinomas and high-grade serous carcinomas with poor prognosis and is absent in the other type I neoplasms, joining molecularly aggressive type I and type 2 tumors (Ayhan, Kuhn et al. in press). This model is rather a meaningful etiopathogenetic representation, that groups different histological types into two broad categories combined for clinical utility, therapeutic and prognostic relevance. An appreciation of the vastly different biology of these tumors should lead to a more informed approach to diagnosis and treatment, thereby reducing the burden of this devastating disease.

**Conclusion**

Recent clinical-pathological, immunohistochemical and molecular genetic studies suggest that most EOCs most probably develop from non-ovarian epithelial cells that implant or home on the ovary. In particular, HGSC may derive from fallopian tubal epithelium either antecedently transformed (STIC cells) or not, LGSC directly from borderline tumors, that in turn seem to take origin from tubal precursors. Finally, endometrioid, clear cell and seromucinous carcinomas potentially arise from endometrium implanted on the ovary, climbing up through the fallopian tube, either in a mature or stem-cell form. As a consequence, recognizing the cell of origin of EOC in the fallopian tube and endometrium instead of the ovary not only redirects the attention outside the ovary as a source of precursor lesions, but also as a site of prophylactic intervention to reduce the burden of this disease. Nevertheless, it designates the fallopian tube as the secret hero or gambler on the ominous game of ovarian cancer by either playing the leading or conveyer role.

Since HGSCs are usually detected in advanced stages, because current screening methods with CA125 and transvaginal ultrasound do not allow to predate the diagnosis of HGSC, they have inauspicious course (68). This new knowledge may allow discovery of novel biomarkers for early detection of ovarian carcinoma. Moreover, the current approach to prophylaxis for ovarian cancer should be reevaluated in the light of the evolving new paradigm of ovarian carcinogenesis. The current prophylactic intervention for women with a family history of ovarian carcinoma and/or BRCA1-2 mutations is hysterectomy and bilateral salpingo-oophorectomy. The unequivocal demonstration that the HGSC rises up from the fallopian tube would indicate salpingectomy alone as the best prophylactic intervention to prevent the risk of ovarian cancer while avoiding the adverse effect of ovary ablation (iatrogenic menopause), a practice which has started to become common in Canada (i.e. opportunistic bilateral salpingectomy) (69).

Finally, in the light of this novel view, scientists and clinicians should focus on defining the biological mechanisms that lead the Müllerian epithelia to sit into the ovary and give rise to EOC, including the tubal and ovarian microenvironment factors, that favor full-fledged cancer development. This effort will allow developing reliable biomarkers for early detection of ovarian carcinoma, and identifying the best prophylactic strategies, thereby reducing the burden of this devastating disease.

**References**


