Brief Overview about Ovarian Cancer

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Abstract
Ovarian cancer is a lethal gynaecologic malignancy as more than 70% of women present with advanced-stage disease. The contributing factors were postulated to be excessive gonadotropin and androgen stimulation of the ovary. In the pathogenesis of ovarian cancer, exposure of the ovaries to pelvic pollutants and carcinogens may play a role. Numerous threats and protective factors are recognized in epidemiological and molecular-genetic studies. Ovarian cancer is the second most common gynecologic malignancy in resource-rich countries and the third most common gynecologic malignancy in resource-limited countries (cervical cancer is the most common). Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States.

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Introduction

Ovarian cancer is a lethal gynaecologic malignancy as more than 70% of women present with advanced-stage disease **(1).** The etiology of ovarian cancer is poorly understood. The woman's age at ovulation (early menarche) which decides the lifetime number of her ovulatory cycles is considered an important index of the risk of ovarian cancer.

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The incidence of ovarian cancer rises with age (except for germ cell tumors, functioning ovarian tumors and familial ovarian cancer). It is more common in women with a family history of the disease. The incidence of EOC increases with increasing age. An analysis of data from the Nurses' Health Study found that the risk increased approximately 2 percent for each additional year of age in patients <50 years old and 11 percent in patients ≥50 years old **(3).**

The median age at diagnosis of ovarian cancer is 63 years old (National Cancer Institute, 2018). In patients younger than 20 years of age, germ cell tumors predominate; borderline tumors typically occur in patients in their 30s and 40s; and after age 50 years, EOC predominates **(4).**

For *BRCA1* and *BRCA2* carriers, the median age at diagnosis was 54.0 and 59.5 years, respectively, in a prospective study **(5).**The average age at diagnosis of ovarian cancer is earlier among patients with a hereditary ovarian cancer syndrome than in sporadic cases. The mean age at diagnosis in patients with Lynch syndrome (hereditary nonpolyposis colon cancer [HNPCC]) was 43 and 49 years in two retrospective studies **(5).**

1. **Family History/Genetic Predisposition**

Having a family history of ovarian and breast cancer has been shown to increase a woman's risk of ovarian cancer. Mutations of the BRCA1 and BRCA2 (tumor suppressing genes), and MMR gene are primarily associated with a genetic risk of ovarian cancer, and can increase the risk of ovarian cancer from 1.6% in general population to 40% in BRCA1 mutation , 18% in BRCA2 mutation, and 10% in MMR gene mutation. **(6)**

This genetic link, known as hereditary breast and ovarian cancer syndrome (HBOC), should be considered if a woman has an immediate relative with a diagnosis of ovarian or breast cancer before the age of 50. By the age of 70, 10% to 40% of carriers of these genetic mutations will develop ovarian malignancies. Also linked to ovarian cancer is Lynch syndrome, although this is less common. **(7)**

The Lynch syndrome is characterized by inheritance of a germline mutation in genes of the DNA mismatch repair system namely, MLH1, PMS2, MSH2 or MSH6, which are mutated at different frequencies **(8).**

Lynch syndrome is an autosomal dominant genetic disorder in which there is a genetic mutation that puts one at risk for certain cancers, specifically colorectal cancer, but also increases the risk for other malignancies, including ovarian cancer. **(9).**

Studies suggest that a patient who has one first-degree relative with ovarian cancer has an approximate 5 percent risk of ovarian cancer, a 3.5 percent risk if the patient has one second-degree relative, and a 7 percent risk if the patient has two affected relatives **(10).**

2. **Ethinic back ground**

According to ethnic groups, the highest prevalence is between Caucasian women (12 per 100,000), followed by Hispanic (10.3 per 100,000), African-American (0.4 per 100,000), and Asian women (9.2 per 100,000). Nevertheless, the highest mortality of ovarian cancer is more significant in African populations **(11).**

3. **Ovulation**

Ovulation also has a direct link to the risk of ovarian cancer. Studies have shown that the more ovulatory cycles a woman complete, the higher her risk of ovarian cancer. **(12).**

This may be because of the pro-inflammatory response of the distal fallopian tubes during ovulation, which promotes malignant ovarian tendencies. **(12).**

It is then correct to assume that factors that interrupt ovulation, such as birth control use, pregnancy, breastfeeding, and early menopause, can decrease a woman's risk of ovarian cancer. **(13).**

4. **Reproductive factors**

Ovarian cancer is associated with low parity and infertility.Early menarche and late menopause increase the risk of ovarian cancer **(14).**

5. **Endometriosis**

Endometriosis has been linked to some epithelial ovarian cancers. Endometriosis associated epithelial ovarian cancers tend to develop in younger women and have a better overall prognosis, however, there is no evidence that shows that removal of endometriosis lesions will decrease a woman's chances of developing ovarian cancer. **(15)**

6. **Dietary Factors**

Smaller studies have shown a link between dietary fiber intake and its correlation with the prevalence of ovarian cancers. It was conducted a study that showed increased intake of dietary fiber led to a significant reduction in the incidence of ovarian cancer. **(16)**

A decrease in the risk of epithelial ovarian cancer is linked to a diet high in soy. Additionally, low levels of vitamin D have been associated with an increased risk of developing ovarian cancer. **(17)**

7. **Ethnicity/Race**

Certain ethnic backgrounds have also been shown to have an increased genetic risk of developing ovarian cancer, specifically Jewish, French Canadian, Dutch, and those of Icelandic descent. **(18)**

8. **Asbestos**

A meta-analysis of 18 cohort studies found that exposure to asbestos was associated with an increased risk of death from EOC **(19).**

9. **Pelvic radiation**

A history of pelvic radiation for treatment of primary rectal carcinoma may increase the risk for developing ovarian cancer, although the overall incidence is small. In one cohort study including over 20,000 female patients with rectal cancer, treatment with radiotherapy plus surgery compared with surgery alone was associated with an increase in ovarian cancer (0.98 versus 0.29 percent, adjusted HR 2.08, 95% CI 1.22-3.56) after a five-year latency period **(19).**

Unlikely or controversial risk factors:

1. **Obesity**

In two systematic reviews, high body mass index appeared to modestly increase ovarian cancer risk (odds ratios [OR] 1.3 and 1.1 **(19).**

2. **Polycystic ovary syndrome**

Systematic reviews regarding risk of ovarian cancer in patients with polycystic ovary syndrome (PCOS) are inconclusive **(20).**

3. **Cigarette smoking**

In a systematic review, current or past smoking appeared to increase the risk of mucinous ovarian cancer (relative risk [RR] 2.1, 95% CI 1.7-2.7) but not other types of EOC (serous, endometrioid, clear cell).The risk increased with increasing levels of cigarette smoking. Smoking also decreased survival in patients with ovarian cancer **(20).**Confounders include an increased prevalence of infertility and obesity in patients with PCOS.

4. Alcohol intake

A meta-analysis found no association between alcohol intake and the risk of EOC **(20).**

5. Diabetes mellitus

Meta-analyses have reported an association between diabetes and ovarian cancer RR 1.17, 95% CI 1.02-1.33 **(20).**

I. Epithelial ovarian tumors

The commonest tumours, constituting about 60-70%of all ovarian tumors and >90% of ovarian cancer. They originate from the ovarian epithelium. Based on the proliferation of the epithelium composing the tumor, depth of invasion, and the epithelial histotype, the Epithelial Ovarian Cancer is sub-classified into benign, borderline, and malignant. According to the histology, the Malignant Epithelial Ovarian Cancer is divided into Serous tumours which are the commonest and subdivided into High-grade serous ovarian cancer (HGSC) and Low-grade serous ovarian carcinomas (LGSC), Endometrioid ovarian carcinomas (EC),Clear cell carcinomas (CCC), and Mucinous carcinomas (MC) (Mungenast & Thalhammer, 2014). Other less common epithelial malignant tumors are e.g. carcinosarcoma, mixed carcinoma, and undifferentiated carcinoma are rare **(21).**

Epithelial ovarian malignancies (which account for the majority of ovarian cancers) are divided into two categories: type I and type II tumors. **(21).**

Type I tumors are thought to be caused from continual ovulation cycles, inflammation, and endometriosis. Having endometriosis is believed to increase a woman's risk of ovarian cancer and is associated with 5% to 15% of all epithelial ovarian cancers. **(21).**

Unfortunately, type II tumors are commonly associated with fatal outcomes; these cancers are usually diagnosed later and are often linked to the genetic mutations of the BRCA genes and p53 mutations, another tumor suppressing gene. One theory is that these tumors have migrated from the fallopian tubes, the point of origin for these cancers. **(21).**

1.serous epithelial carcinoma

When speaking about the serous subtype of epithelial ovarian cancers specifically, percentages can be further broken down between HGSC and LGSC, with HGSCs making up 90% of all serous tumor types, and LGSCs making up 10%. These two types of serous carcinomas have different molecular profiles, clinical presentations, and even prognosis; LGSCs have a better prognosis, with the expected survival time being significantly longer compared with those with HGSCs (as well as clear cell or mucinous types). **(22)**

A) High-grade serous carcinoma

High-grade serous carcinoma (HGSC) is the most common type of ovarian cancer and accounts for approximately 70 to 80 percent of all malignant ovarian neoplasms. The peak age range is 45 to 65 years with a mean of 57 years **(1).**

Most HGSC is diagnosed at an advanced stage (stage III or IV) and has a poor overall prognosis. HGSC that is confined to the ovary at diagnosis is rare (<10 percent) **(15).**

High grade serous carcinomas arises from fimbria of the fallopian tube . This group was formerly thought to arise spontaneously on the ovarian or peritoneal surface. Although. the neoplastic transformational trigger of the fallopian tube cells is unclear, serous tubal intracpithdial carcinoma (STIC) is a precursor condition . STIC devdops several years before initiation of ovarian carcinoma, yet metastases follow rapidly thereafter **(3).**

High-grade serous tumors are aggressive, and diagnosed at advanced stages more than three quarters of the time, and display a greater value of extra ovarian disease and significant ascites. These tumors account for 90 percent of ovarian cancer deaths **(22).**

B) Low-grade serous carcinoma

Like HGSC, LGSC is typically diagnosed at an advanced stage, and consequently the long-term prognosis is poor. However, these neoplasms are biologically distinct from HGSC and are slow-growing, indolent neoplasms with relative insensitivity to platinum-based chemotherapy **(23).**

In contrast to high-grade serous carcinoma (HGSC), low-grade serous ovarian carcinoma (LGSC) is uncommon and accounts for fewer than 5 percent of all cases of ovarian carcinoma LGSC develops either from benign ovarian lesions that implant on the ovary and subsequently undergo malignant transformation or from a portion of the ovarian surface epithelium that becomes entrapped within the ovarian cortex. This trapped cortical inclusion cyst undergoes mullerian metaplasia and is exposed to hormone and inflammatory stimuli that induces DNA damage and mutations. LGSC is often found along with a noninvasive serous borderline component. Borderline serous neoplasms are more common than LGSC, and LGSC most likely represents progression of a serous borderline neoplasm **(23).**

ENDOMETRIOID CARCINOMA

Endometrioid carcinoma of the ovary accounts for approximately 10 percent of all ovarian carcinomas. Endometrioid carcinoma presents most frequently in female patients in their 40s and 50s, with a mean patient age of 56 years. Endometrioid carcinomas are most often identified at an early stage (unlike serous carcinomas), consequently these patients have a much better prognosis. Endometrioid carcinomas tend to be relatively chemosensitive (unlike low-grade serous or clear cell carcinoma), which also contributes to the better prognosis relative to other subtypes of ovarian carcinoma. Primary ovarian endometrioid adenocarcinoma is typically low-grade. However, high-grade endometrioid carcinomas are morphologically and molecularly indistinguishable from high-grade serous carcinoma (HGSC), with immunophenotypic and gene profiling studies suggesting that high-grade endometrioid carcinoma is not a distinct tumor type, but rather a subtype of HGSC **(23).**

Ovarian endometrioid carcinoma is often associated with and believed to arise from endometriosis (up to 42 percent of patients have evidence of ovarian or pelvic endometriosis) **(23).**

Endometrioid ovarian carcinoma is associated with carcinoma of the endometrium in 15 to 20 percent of cases **(23).**

CLEAR CELL CARCINOMA

Clear cell carcinoma accounts for approximately 5 to 10 percent of all ovarian carcinomas in North America and presents most commonly in perimenopausal patients in their late 40s or 50s.Clear cell carcinoma constitutes a larger percentage of ovarian cancers in East Asia, although it is unclear whether this is due to genetic or environmental factors. Like endometrioid carcinoma, ovarian clear cell carcinoma often presents at an early stage (stage I or II) and has a relatively good prognosis due to the absence of distant metastases. However, when clear cell carcinoma presents at an advanced stage, it has a worse prognosis than serous or endometrioid carcinoma. This is because clear cell carcinoma is not as sensitive to platinum-based chemotherapy as the other histologic subtypes **(24)**

MUCINOUS CARCINOMA

Mucinous carcinoma accounts for 3 to 4 percent of primary ovarian cancers . These neoplasms most often present in perimenopausal patients in their late 40s to early 50s, although they have been reported in patients as young as 14 and old as 87 (Lee & Scully, 2000) Nearly all mucinous carcinomas of the ovary present with early stage disease, usually stage I. When including all types of mucinous neoplasms, they account for 10 to 15 percent of all ovarian neoplasms. Approximately 80 percent are benign mucinous cystadenomas, and the majority of the rest are mucinous borderline neoplasms. In addition, most mucinous carcinomas within the ovary are metastases, frequently from the gastrointestinal tract **(25)**

Transitional cell carcinoma

Historically, the definition of transitional cell carcinoma of the ovary has been a neoplasm composed of epithelial elements histologically resembling urothelium that lack a component of a benign or borderline Brenner tumor **(25)**

Carcinosarcoma

Carcinosarcoma, also referred to as a malignant mixed müllerian tumor (MMMT), comprises between 2 to 7.5 percent of ovarian carcinomas with a mean age of presentation of 75 years **(25)**

Undifferentiated/dedifferentiated carcinoma

The World Health Organization defines undifferentiated ovarian carcinoma as a primary ovarian carcinoma with little to no differentiation and dedifferentiated carcinoma as a carcinoma with an undifferentiated and a differentiated component (a lower grade endometrioid component, or less often, a serous component) **(20).**

Overview of borderline neoplasms

In the early 1970s, the histologic category of borderline ovarian epithelial neoplasms was introduced to describe a group of neoplasms that did not display overt malignant features (invasion), but that occasionally had intraperitoneal spread. Borderline neoplasms account for an estimated 14 to 15 percent of all primary ovarian neoplasms and 15 to 20 percent of ovarian serous neoplasms **(25)**

Serous borderline neoplasm

Approximately 10% of all ovarian serous tumors fall into the category of a tumor of low malignant potential or borderline tumor , and 50% occur before the age of 40 years. Serous borderline neoplasm is the most common histologic subtype and accounts for approximately 65 percent of borderline ovarian neoplasms. The mean age of presentation is 35 to 40 years of age, although this can range widely **(26).**

The criteria for the diagnosis of serous borderline tumors are as follows **(26).**

1. Epithelial hyperplasia in the form of pseudostratification, tufting, cribriform, and micropapillary architecture.
2. Mild nuclear atypia and mild increased mitotic activity.
3. Detached cell clusters.
4. Absence of destructive stromal invasion (i.e., without tissue destruction).

Serous borderline tumors that are composed of an exuberant micropapillary architecture are designated as serous borderline tumors with micropapillary features ; these tumors are more frequently bilateral, exophytic, and high stage than the usual serous borderline tumor.

It should be emphasized that up to 40% of serous borderline tumors are associated with spread beyond the ovary, but high-stage disease does not necessarily warrant a diagnosis of an invasive carcinoma. The diagnosis of a serous borderline tumor versus serous carcinoma is based on the histologic features of the primary tumor **(26).**

Up to 10% of women with ovarian serous borderline tumors and extraovarian implants may have invasive implants (i.e., low-grade serous carcinoma), and these can behave more aggressively **(26).**

The 5-year overall survival for women with invasive implants (low-grade serous carcinoma) is about 50% if stringent criteria are applied. Most implants are noninvasive (Michael & Roth, 1986). In the noninvasive implants, papillary proliferations of atypical cells involve the peritoneal surface and form smooth invaginations **(26).**

Borderline serous tumors may harbor foci of stromal microinvasion. Most patients are young and their tumors are International Federation of Obstetrics and Gynecology (FIGO) stage I. Stromal microinvasion is increased about ninefold in pregnant women with serous borderline tumors. The presence of stromal microinvasion is associated with lymphovascular space invasion in the primary ovarian tumor (and likely represents a form of true stromal invasion), but it is not associated with an aggressive clinical course, and patients with this finding should be managed in the same way as patients without stromal microinvasion. The 10-year survival rate is 95 to 100 percent, although late recurrences are not uncommon (Hart, 2005). Prognosis is still excellent

despite presence of peritoneal implants and regional lymph node involvement in up to 35 percent of patients (27)

Mucinous borderline neoplasm

Borderline mucinous neoplasms are nearly always confined to the ovary, unlike serous borderline neoplasms. The mucinous tumor of low malignant potential is often difficult to diagnose. Although it is common to find a rather uniform pattern from section to section in the serous borderline tumor, this is not true in the mucinous tumors. Well-differentiated mucinous epithelium may be seen immediately adjacent to a poorly differentiated focus. It is important to take multiple sections from many areas in the mucinous tumor to identify the most malignant alteration (27)

ENDOMETRIOID BORDERLINE NEOPLASM

As with serous and mucinous neoplasms, a neoplasm with a biologic potential between cystadenomas/adenofibromas and invasive endometrioid adenocarcinoma of the ovary with an endometrioid morphology has been reported. The endometrioid tumor of low malignant potential has a wide morphologic spectrum. Tumors may resemble an endometrial polyp or complex endometrial hyperplasia with glandular crowding. When there are back-to-back, architecturally complex glands with no intervening stroma, the tumor is classified as a welldifferentiated endometrioid carcinoma. Some borderline endometrioid tumors have a prominent fibromatous component. In such cases, the term adenofibroma is used to describe them **(28).**

- **Borderline Brenner Tumors**

Borderline Brenner Tumors Proliferative Brenner tumors were previously subclassified as proliferating tumors (those tumors that resemble low-grade papillary urothelial carcinoma of the urinary bladder) and borderline tumors (those tumors that resemble high-grade papillary urothelial carcinoma), these groups of tumors are now classified as borderline Brenner tumors **(28).**

II.Sex cord-stromal tumors

The incidence of SCSTs was 0.2 per 100,000 females (Quirk & Natarajan, 2005). most SCSTs have no association with the *BRCA* germline mutations or a genetic predisposition to breast cancer. An exception is granulosa cell tumors, which appear to be more common in patients who have a family history of breast or ovarian cancer. Ovarian SCSTs are less common than tumors of epithelial cell and germ cell origin. Benign ovarian SCSTs account for <4 percent of ovarian benign neoplasms, and malignant ovarian SCSTs account for <8 percent of ovarian malignant neoplasms.Ovarian sex cord-stromal tumors (SCST) are a group of benign and malignant neoplasms that develop from the sex cord (eg, Sertoli cell tumor, granulosa cell tumor) or stromal cells (eg, fibroma, thecoma, Leydig cell tumor) or both (eg, Sertoli-Leydig cell tumor). Some ovarian SCSTs produce steroid hormones, particularly androgens or estrogens, and thus may present with signs of virilization or estrogen excess **(28).**

III. Germ cell tumors of the ovary (GCTs)

They originate from primitive germ cell migrating from endoderm of hind gut at 7week embryo to the ovary. The Germ cell ovarian tumors secrete various biological markers

such as the AFP secreted by the Yolk sac tumor (endodermal sinus tumor), while choriocarcinoma produces βHCG. and Dysgerminomas secrete lactate dehydrogenase(LDH) and HCG.The ovarian malignant germ cell tumors (OMGCTs) account < 5% of all ovarian cancers (Ulbright, 2005). OGCTs are found primarily in young females between 10 and 30 years of age, representing 70 percent of ovarian neoplasms in this age group. Among **malignant** OGCTs, dysgerminoma, immature teratoma, yolk sac tumors, and mixed germ cell tumors account for 90 percent of cases **(29).**

Metastatic ovarian cancers

A lot of extra-genital organs tumors e.g. stomach cancer, or breast cancer are metastasized to the ovary. Krukenberg tumors are ovarian metastatic tumors from the gastrointestinal tract malignancies. They represent 1– 2% of all ovarian tumors **(30).**Approximately 80% of these tumors are bilateral. The gastric signet ring cell carcinoma of the stomach is the most common primary tumor of Krukenberg tumor cases (70%), followed by Carcinomas of the colon, the appendix, and the breast **(30).**

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References:

[1] Nezhat, C., King, L. P., Cho, J., Vu, M., Vang, N., & Nezhat, F. (2021). Video Laparoscopic Management of Adnexal Masses with or Without Robotic Assistance. In Robotic Surgery (pp. 1259-1266). Springer, Cham.

[2] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.

[3] Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-1999: results of the EUROCARE-4 study. Lancet Oncol 2007; 8:773-83

[4] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. National Cancer Institute (Bethesda, MD), Apr 2014. http:// seer.cancer.gov/csr/1975_2011/.

[5] Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305:2295-303

[6] Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 2008;18:414-20.

[7] Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327-40..

[8] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. (2015) SEER Cancer Statistics Review, 1975-2012. Vol. 2015. National Cancer Institute: Bethesda, MD

[9] Bristow RE, Chang J, Ziogas A, Anton-Culver H (2013) Adherence to treatment guidelines for ovarian cancer as a measure of quality care. Obstet Gynecol 121(6): 1226–1234

[10] Bristow RE, Chang J, Ziogas A, Randall LM, Anton-Culver H (2014) High volume ovarian cancer care: survival impact and disparities in access for advanced-stage disease. Gynecol Oncol 132(2): 403–410.

[11] Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, Kanayama S, et al. (2008) A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 18(3): 414–420.

[12] Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT, et al. (2011) Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 305(22): 2295–2303

[13] Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN, et al. (2015) Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 387: 945–956.

[14] Kurtz AB, Tsimikas JV, Tempany CM et al (1999) Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging correlated with surgery and histopathologic analysis–report of the Radiology Diagnostic Oncology Group. Radiology 212:19–27.

[15] Kinkel K, Hricak H, Lu Y, Tsuda K, Filly RA (2000) US characterization of ovarian masses: a meta-analysis. Radiology 217:803–811

[16] Spencer JA, Forstner R, Hricak H (2008) Investigating women with suspected ovarian cancer. Editorial Gynecol Oncol 108:262–264.

[17] Lucidarme O, Akakpo JP, Granberg S et al (2010) A new computer-aided diagnostic tool for non-invasive characterisation of malignant ovarian masses: results of a multicentre validation study. Eur Radiol 20:1822–1830.

[18] Outwater EK, Dunton CJ (1995) Imaging of the ovary and adnexa: clinical issues and applications of MR imaging. Radiology 194:1–18.

[19] Spencer JA, Forstner R, Cunha TM, Kinkel K, ESUR female imaging sub-committee (2010) ESUR guidelines for MR imaging of the sonographically indeterminate adnexal mass: an algorithmic approach. Eur Radiol 20:25–35.

[20] Sohaib SA, Mills TD, Sahdev A et al (2005) The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clin Radiol 60:340–348.

[21] Adusumilli S, Hussain HK, Caoili EM et al (2006) MRI of sonographically indeterminate adnexal masses. AJR Am J Roentgenol 187:732–740.

[22] Kaijser J. Towards an evidence-based approach for diagnosis and management of adnexal masses: findings of the International Ovarian Tumour Analysis (IOTA) studies. Facts Views Vis Obgyn 2015; 7: 42–59.

[23] Timmerman D, Testa AC, Bourne T, Ferrazzi E, Ameye L, Konstantinovic ML, Van Calster B, Collins WP, Vergote I, Van Huffel S, Valentin L; International Ovarian Tumor Analysis Group. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. J Clin Oncol 2005; 23: 8794–8801.

[24] Timmerman D, Testa AC, Bourne T, Ameye L, Jurkovic D, Van Holsbeke C, Paladini D, Van Calster B, Vergote I, Van Huffel S, Valentin L. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol 2008; 31: 681–690.

[25] Kaijser J, Bourne T, Valentin L, Sayasneh A, Van Holsbeke C, Vergote I, Testa AC, Franchi D, Van Calster B, Timmerman D. Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. Ultrasound Obstet Gynecol 2013; 4: 9–20.

[26] Kaijser J, Sayasneh A,Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, Van Calster B. Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis. Hum Reprod Update 2014; 20: 449–462.

[27] Van Holsbeke C, Van Calster, Bourne T, Ajossa S, Testa AC, Guerriero S, Fruscio R, Lissoni AA, Czekierdowski A, Savelli L, Van Huffel S, Valentin L, Timmerman D. External validation of diagnostic models to estimate the risk of malignancy in adnexal masses. Clinical Cancer Res 2012; 18; 815–825.

[28] Van Calster B, Van Hoorde K, Valentin L, Testa AC, Fischerova D, Van Holsbeke C, Savelli L, Franchi D, Epstein E, Kaijser J, Van Belle V, Czekierdowski A, Guerriero S, Fruscio R, Lanzani C, Scala F, Bourne T, Timmerman D; International Ovarian Tumour Analysis IOTA Group. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicenter diagnostic study. BMJ 2014; 349: g5920.

[29] Van Calster B, Van Hoorde K, Froyman W, Kaijser J, Wynants L, Landolfo C, Anthoulakis C, Vergote I, Bourne T, Timmerman D. Practical guidance for applying the ADNEX model from the IOTA group to discriminate between different subtypes of adnexal tumors. Facts Views Vis Obgyn 2015; 7: 32–41.

[30] Sherman ME, Mink PJ, Curtis R, Cote TR, Brooks S, Hartge P, Devesa S. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer 2004; 100: 1045–1052.