Endometriosis , Tumor Marke
&
Ovarian Cancer

Atefeh Gorgin. Md

Fellowship In Advanced Laparoscopic Surgery

ENDOMETRIOSIS AND CANCER

- Endometriosis is a common disease affecting 10 to 15% of women of reproductive age.
- Endometriosis is a complex disease, and is an estrogen-dependent disease, its origin remains unclear.
- Ovarian endometriosis is one of the leading causes of female infertility and is a known risk factor for the development of ovarian cancer. An association between endometriosis and cancer was reported as early as the **1920s** in english publications.
- Ectopic endometrium undergoes malignant transformation with a frequency similar to its eutopic counterpart
- Ovarian cancer is the second most lethal gynecological malignancy
- Many reports clearly reveal that **not all types** and **not all cases** of endometriosis transform to malignancy.

ENDOMETRIOSIS AND CANCER

- Increased risk of ovarian cancers in women with endometriosis varying between **1.3 and 1.9.**
- The tumour biomarker **ca125** has been used as the primary ovarian cancer marker for the past four decades.

- Endometriosis :**A precursor of ovarian cancer**, especially **Clear Cell Carcinoma** (OCCC) and **Endometrial Carcinoma**
- Association to **the endometrioid** and **clear-cell** **histologic types of ovarian cancer**, are categorized as **endometriosis-associated ovarian cancers (eaoc).**

- Evidence for an association with **melanoma** and **non-hodgkin lymphoma** has been reported but needs to be verified, whereas an increased risk for other gynecologic cancer types is not supported.

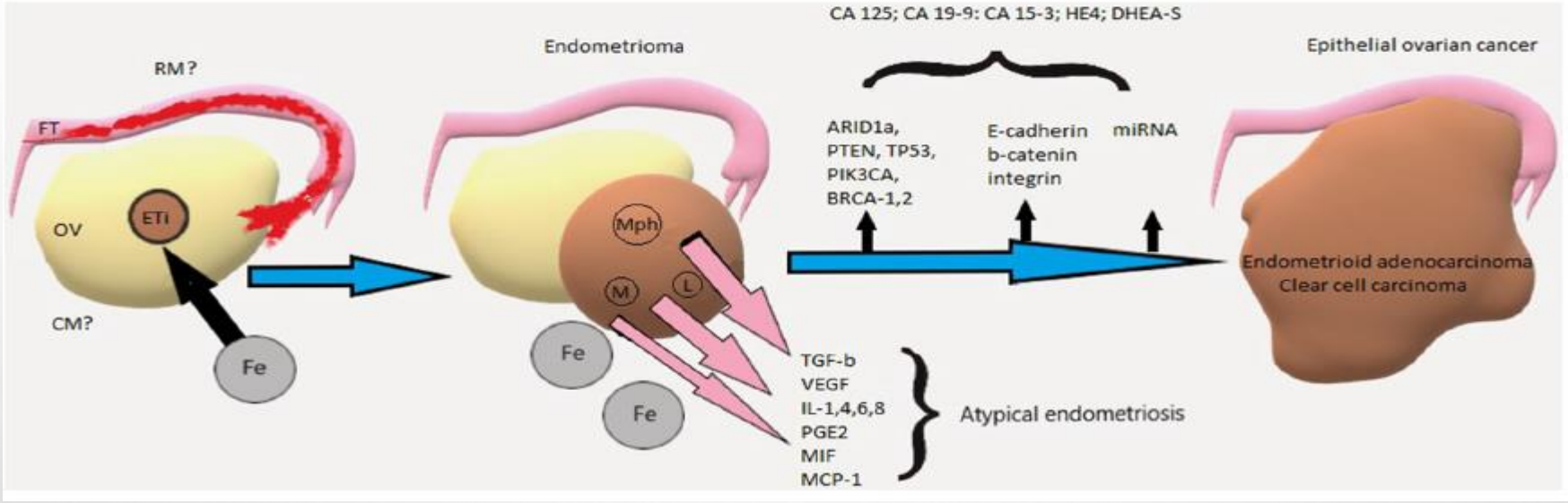
Adv Ther (2020) 37:2580–2603
https://doi.org/10.1007/s12325-020-01363-5

REVIEW

Malignant Transformation and Associated Biomarkers of Ovarian Endometriosis: A Narrative Review

- Despite intensive research extending even to the molecular level, the origin, natural history, malignant transformation, and laboratory management of endometriosis and related diseases are not yet clearly defined.
- **Early laboratory diagnoses** of endometriosis, its atypical form, and **endometriosis-associated ovarian tumors** are important problems.

Many biomarkers have been investigated that are based on molecular pathways from cell surface and nuclear macromolecules



Some serum biomarkers are **elevated in the case of endometriosis** while subsequent histological examination shows benign-looking endometriotic glands and stroma.

It is justifiable to conjecture that there is a developmental time lag between cell atypia and tissue atypical changes.

Subtle histological changes in endometriosis epithelial cells that precede atypical transformation but without any correlation between atypical changes and biomarker investigations

Ca-125:

- Cancer antigen-125 (ca-125) is a traditional biomarker that originates from the coelomic epithelia of the uterus, fallopian tubes, and ovaries in the pelvic cavity .
- This biomarker has been **associated with ovarian epithelial cancers** and found to be elevated in greater than **80%** of ovarian epithelial tumors .
- A positive **association between advanced stages of endometriosis** and **elevated ca-125** in the peritoneal fluid has been reported .
- Ca-125 levels **> 30u/ml** can be used as rule-in criteria for diagnosis .
- It is uncommon for ca-125 to reach above 100u/ml in women with endometriosis ,but can be elevated as high as **10,000u/ml in cases of endometrioma rupture** or when **the omentum is involved** .
- Ca125 has played an important role in the screening, treatment, and follow-up phases of ovarian cancer management.
- **Ca125**, human epididymis protein 4 **(He4)** is the most promising tumour biomarker for ovarian cancer. the two biomarkers **have similar sensitivities.**
- **He4** measurements exhibit a significantly cancer **higher specificity** than ca-125 (93% vs. 78%)
- Ca125, ca72-4, ca15-3, and macrophage colony-stimulating factor (m-csf) values were used as input for ann. the ann was found to be **superior to ca125 alone for detecting invasive early-stage ovarian**
- Ca125 is still superior to the majority of novel biomarkers in postmenopausal women, including He4

Hamed et al. Diagnostic Pathology 2013, 8:11
http://www.diagnosticpathology.org/content/8/1/11

DIAGNOSTIC PATHOLOGY

RESEARCH Open Access

Significance of HE4 estimation in comparison with CA125 in diagnosis of ovarian cancer and assessment of treatment response

Elham O Hamed[1*], Hydi Ahmed[1], Osama B Sedeek[4], Abeer M Mohammed[1], Ali A Abd-Alla[2] and Hazem M Abdel Ghaffar[3]

- Human epididymis protein 4 **(He4)** is a novel and specific biomarker for ovarian cancer concentrations were significantly higher in the ovarian cancer patients ($p = 0.001$) **serum He4** and **Ca125** ($p < 0.001$ respectively).
- He4 demonstrated comparable diagnostic performances to ca125 as a tumor marker for detecting ovarian cancer.
- **He4** was more **sensitive** in detecting **early stages of ovarian cancer** and **more specific**.
- He4 improves the utility of Ca125 as a tumor marker in ovarian cancer, and using both markers simultaneously increases the tumor marker sensitivity.
- The use of this **combination** might enable to improve detection of ovarian cancer as compared with use of either marker alone for the discrimination of benign from malignant ovarian lesions.

ATYPICAL ENDOMETRIOSIS

- Atypical endometriosis was first described by czernobilsky and morris in 1979.
- **repetitive damage and inflammation** in ectopic endometrial foci result in the development of atypical endometriosis and eventually into endometriosis associated ovarian neoplasms.
- **Atypical endometriosis was found in 36% of occc &** in **23% of endometrial associated adenocarcinoma** with direct progression into eaoc,
- progression of atypical endometriosis into eaoc **is similar to that of atypical endometrial hyperplasia**, thus demonstrating its function as premalignant marker .
- Occc **and** eaoc of the ovary are **two of the most common malignant neoplasia associated with endometriosis**.
- Occc is the **second most common type of ovarian cancer** in the world

Mecanism:

-Atypical epithelial cells arise from **previous endometriotic lesions** in the ovary prior to progressing into cancer.

-Non-cystic ectopic endometrial implants generate fibroadenomas, which develop atypical cells that develop into occc

- **Eaoc** comprises **20% of all ovarian cacer** is the **most common form of malignancy related to endometriosis**
- There is a close association between atypical endometriosis lesions and eaoc.

- That ectopic endometrial implantation in the peritoneal cavity releases higher levels of **ca-125**, resulting in **levels above 100u/ml .**

- The specificity of Ca-125 levels is enhanced when evaluated in coordination with He-4 levels.

- khodaverdi et al noted that elevated ca-125 and normal He-4 can be indicative of endometrioma. Generally, **He-4 is elevated** in **malignancy** and has been shown to **be normal in the case of an endometrioma**

- **The combined use of ca-125 and He-4** may be key to effectively diffrentiating ovarian malignancies and endometriosis in the future.

So et al. J Ovarian Res (2021) 14:110
https://doi.org/10.1186/s13048-021-00865-2

Journal of Ovarian Research

RESEARCH Open Access

Association between atypical endometriosis and ovarian malignancies in the real world

Kyeong A So[1,2], Sung Ran Hong[3,4], Nae Ri Kim[1], Eun Jung Yang[1], Seung-Hyuk Shim[1], Sun Joo Lee[1] and Tae Jin Kim[1,2*]

- Atypical endometriosis is considered to have **premalignant potential**, is characterized by **dysplastic features with cellular atypia**, and is different from typical endometriosis.
- Atypical endometriosis represents a transition from endometriosis to carcinoma that may occur in the process of **endometriotic tissue undergoing chronic inflammation and oxidative stress**.
- **Atypical endometriosis** is most frequently associated with clear cell carcinoma and endometrioid adenocarcinoma.
- **To identify the risk of ovarian malignancy** and **manage patients with endometriosis**, diagnosing atypical endometriosis and recognizing its precancerous potential are important.
- The large size of atypical endometriotic cyst was associated ovarian malignancy ($p = 0.025$)
- It is not necessary for patients with endometriosis to be screened for cancer, if they are diagnosed with atypical endometriosis, **they should be counseled for the potential risk of progression to endometriosis-associated ovarian malignancy**

OPEN

Clinical Use of Cancer Biomarkers in Epithelial Ovarian Cancer

Updated Guidelines From the European Group on Tumor Markers

- **EUROPEAN GROUP ON TUMOR MARKERS STATEMENT**
- Screening for ovarian cancer based on Ca125 **is not recommended** among asymptomatic women due to lack of sensitivity both for stage i disease and for **mucinous epithelial ovarian tumors**.
- Ca125 also lacks specificity, especially for premenopausal women.
- **(LOE I, SOR B)**

- **EUROPEAN GROUP ON TUMOR MARKERS STATEMENT**
- The **RMI** calculated either as RMI 1 or as RMI 2 is recommended for differential diagnosis of non-malignant and malignant pelvic masses in postmenopausal women.
- **(LOE II-III, SOR B)**

At present, ca125 remains the most important biomarker for epithelial ovarian cancer, excluding tumors of mucinous origin.

- **EUROPEAN GROUP ON TUMOR MARKERS STATEMENT**
- A change in sequential measurements during primary treatment is recommended as prognostic indicator for response to treatment.
- **(LOE III/IV, SOR B)**

- **EGTM STATEMENT**
- He4 measurements, either alone or in combinations nwith ca125, as in ROMA, may be considered for differential diagnosis of pelvic masses especially in premenopausal patients.
- **(LOE III, SOR B)**

- A ca125 is recommended for monitoring of primary therapy and post-therapy surveillance.
- A ca125 decrement is defined as at least a 50% reduction in ca125 levels from a pre-treatment sample.

- The decrement must be confirmed and maintained for at least 28 days.
- A ca125 decrement may also be defined by a 50% decrease over four measurements or a 75% decrease over three measurements.

Original Article
Diagnostic Immunology
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https://doi.org/10.3343/alm.2020.40.1.40
ISSN 2234-3806 · eISSN 2234-3814
ANNALS OF LABORATORY MEDICINE

Clinical Usefulness of Cancer Antigen (CA) 125, Human Epididymis 4, and CA72-4 Levels and Risk of Ovarian Malignancy Algorithm Values for Diagnosing Ovarian Tumors in Korean Patients With and Without Endometriosis

- Tumor markers are useful for detection
- **He4** levels and **ROMA** values were significantly higher in the malignant group than in the borderline group.
- **ROMA** value had the highest auc for distinguishing the malignant and borderline groups from the benign group in premenopausal (0.773) and postmenopausal (0.927) patients.
- **Ca125 level was significantly higher in patients with endometriosis** than in those without ($p<0.001$), whereas He4 and Ca72-4 levels were not affected by endometriosis ($p=0.128$ and 0.271, respectively).
- **Conclusions:** **ROMA** value is the best marker to distinguish **malignant and borderline tumors** from benign tumors in pre- and postmenopausal patients.
- He4 and ca72-4 levels provide information on possible ca125 elevation due to endometriosis.

- **Ca125** showed the **highest sensitivity**, and **He4** showed **higher specificity** for diagnosing malignant tumor using the recommended cut-off in premenopausal and postmenopausal patients.

- The significantly higher specificity of He4 than that of ca125 indicates that He4 is less likely to be affected by factors other than the malignancy it self He4 showed better results than Ca125 for monitoring ovarian cancer.

- Numerous reports indicated that combining ca125 with other laboratory and imaging results significantly **improved specificity**

- **He4** has been shown to be the most useful marker for **differential diagnosis of ovarian cancer and endometriosis.**

- **ROMA** value was the best marker to distinguish malignant and borderline tumors from benign tumors in both pre- and postmenopausal patients.
- **He4** and **Ca72-4** can be used in **combination with ca125** to increase the diagnostic sensitivity in premenopausal patients.
- He4 and Ca72-4 provide information on the possibility of ca125 elevation by endometriosis.

JOURNAL OF OBSTETRICS AND GYNAECOLOGY
https://doi.org/10.1080/01443615.2018.1441815

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ORIGINAL ARTICLE

Check for updates

Concomitant endometriosis in malignant and borderline ovarian tumours*

- **Ovarian endometriosis is seen with both malignant and borderline ovarian tumours, the association being significant with borderline tumours..**

- Epidemiologic data suggest that endometriosis has malignant potential.
- Endometriosis and ovarian cancer association does not seem to have a clinical implication.
- The findings of this study revealed that nearly 75% of endometriosis-associated ovarian tumours were of **atypical endometriosis**.

- **Half of endometriosis associated ovarian tumour** cases were of **endometrioid/clear cell** histology and **70% were earlystage**.
- Endometriosis was **significantly associated with borderline ovarian tumours** and the endometriosis- associated malignant ovarian tumours were mostly early stage.

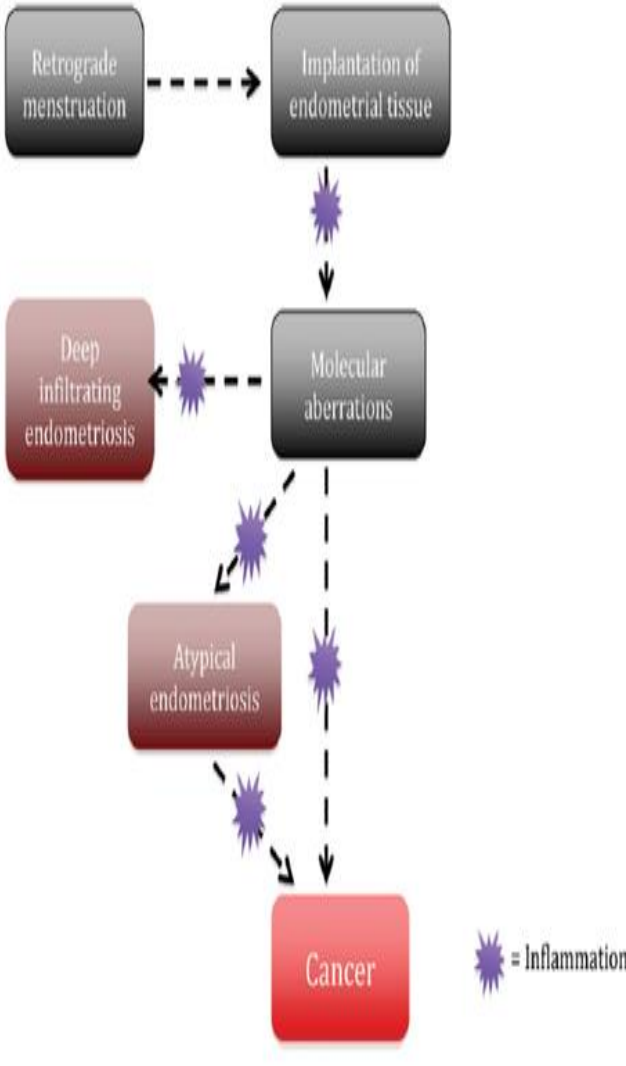
ecancermedicalscience

Endometriosis and endometriosis-associated cancers: new insights into the molecular mechanisms of ovarian cancer development

Amy Dawson[1], Marta Llauradó Fernandez[1], Michael Anglesio[1,2], Paul J Yong[1], and Mark S Carey[1,3]

- the observation that endometriosis is **a cancer precursor** has now been strengthened with the knowledge that **mutations** that are present in endometriosis-associated cancers can be found in adjacent endometriosis lesions.

- Recent genomic studies, placed in context, suggest that **deep infiltrating endometriosis** may represent a benign neoplasm that invades locally but **rarely metastasises**.



- A number of gynaecologic cancers of specific histotypes are thought to originate from endometriosis

- For those women who are having surgery for endometriomas close to **menopause**, unilateral salpingo-oophorectomy may be considered if the endometrioma cannot be completely removed by cystectomy as most cases of eaoc arise from endometriomas.

- Understanding **the molecular biology of endometriosis** will be the key to better treatments for endometriosis and guide future early detection and prevention strategies to further reduce the incidence and mortality of eaocs.

CANCER BIOLOGY & THERAPY
2019, VOL. 20, NO. 7, 1029–1034
https://doi.org/10.1080/15384047.2019.1595278

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RESEARCH PAPER

Check for updates

Endometriosis-associated ovarian cancer is a single entity with distinct clinicopathological characteristics

Qianwen Li*[a], Yue Sun*[b], Xiang Zhang[b], Linping Wang[b], Wenling Wu[b], Meijing Wu[b], Chao Meng[b], and Guoyan Liu[b]

- The eaoc patients were often diagnosed at a younger age, an earlier stage, and related to nulliparity and infertility.

- **Patients with eaoc had a better prognosis than non-eaoc, early stage rather than association with endometriosis may be the driver of survival.**

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2021; 12(22): 6773-6786. doi: 10.7150/jca.61107

Review

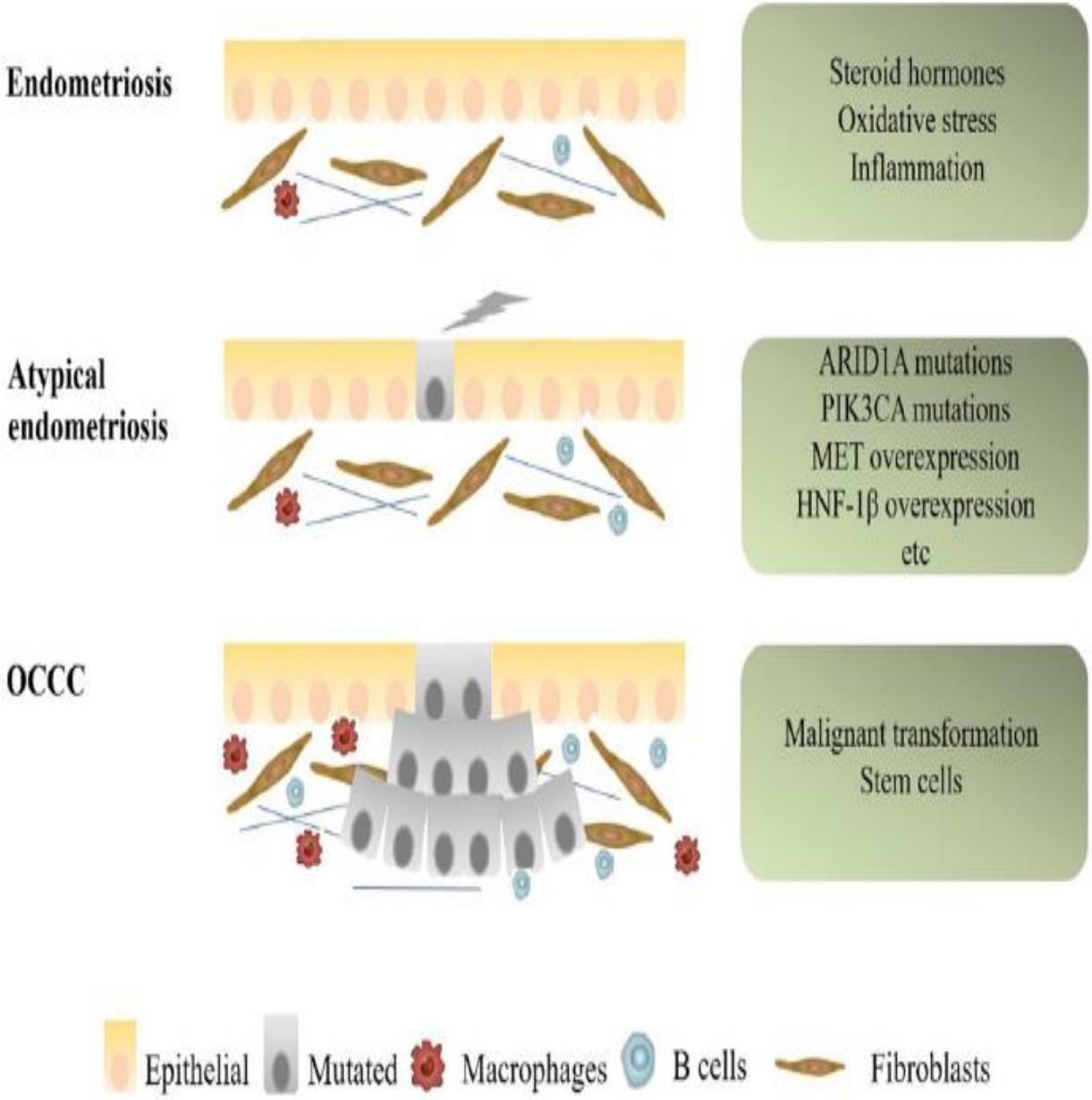
Endometriosis-associated Ovarian Clear Cell Carcinoma: A Special Entity?

Yue Sun[1,2] and Guoyan Liu[1,2]✉

- Although micro-environmental factors such as **oxidative stress**, **immune cell dysfunction**, **inflammation**, **steroid hormones**, and **stem cells** required for **malignant transformation** have been found **in endometriosis**, **the exact carcinogenic mechanism remains unclear.**
- Recent research suggest that many putative driver genes and aberrant pathways including arid1a mutations, pik3ca mutations, met activation, hnf-1β activation, and mirnas dysfunction, play crucial roles in the malignant transformation of endometriosis to occc.

The clinical features of occc are different from other histological types:

- **a large, unilateral pelvic mass**, **thromboembolic vascular complications**
- **easier to be resistant to chemotherapy**
- **worse prognosis**
- **difficult to treat**


Endometriosis
Steroid hormones
Oxidative stress
Inflammation
Atypical endometriosis
ARID1A mutations
PIK3CA mutations
MET overexpression
HNF-1β overexpression
etc
OCCC
Malignant transformation
Stem cells
Epithelial
Mutated
Macrophages
B cells
Fibroblasts

Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

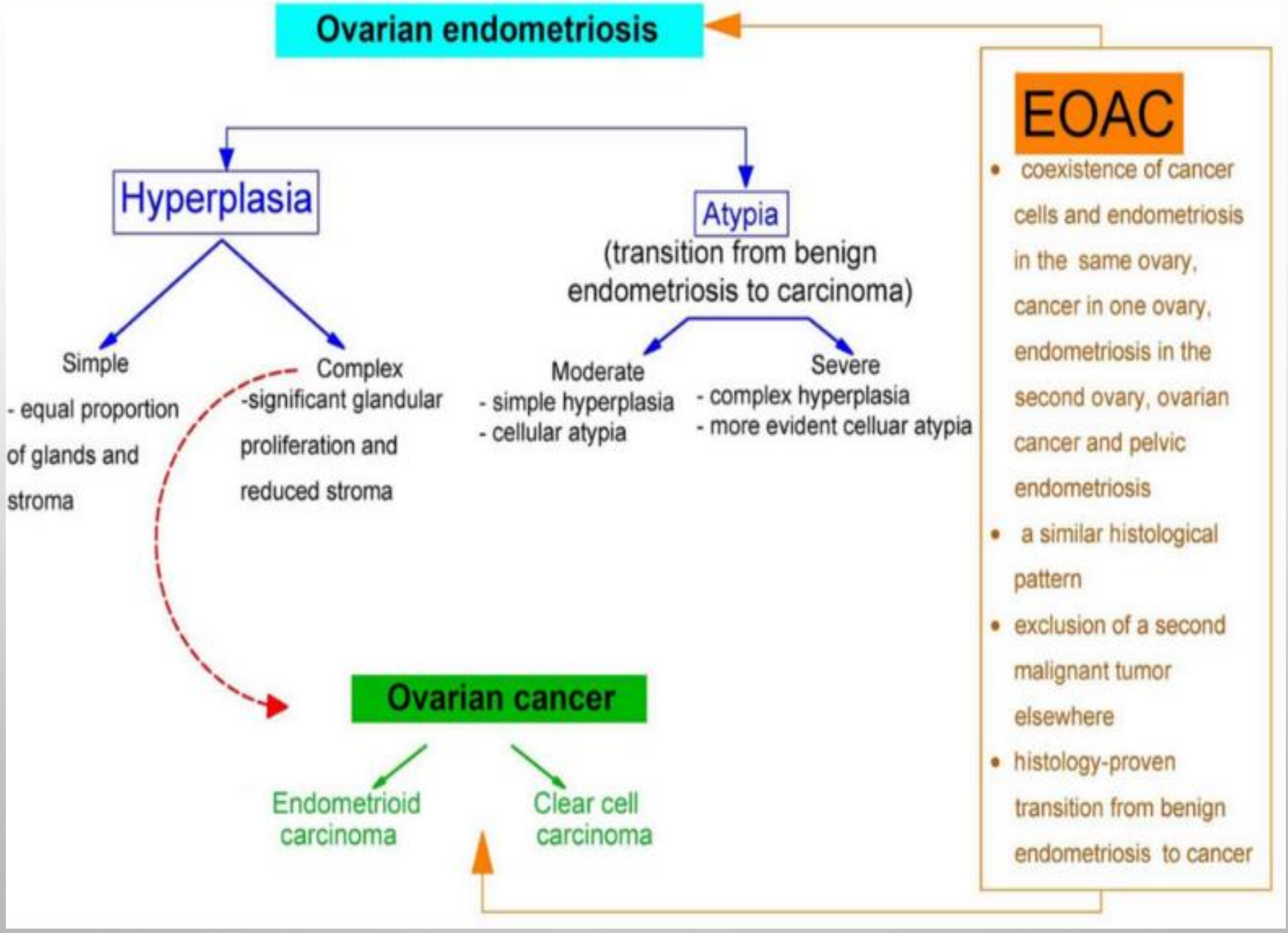
Journal of International Medical Research
49(9) 1–9

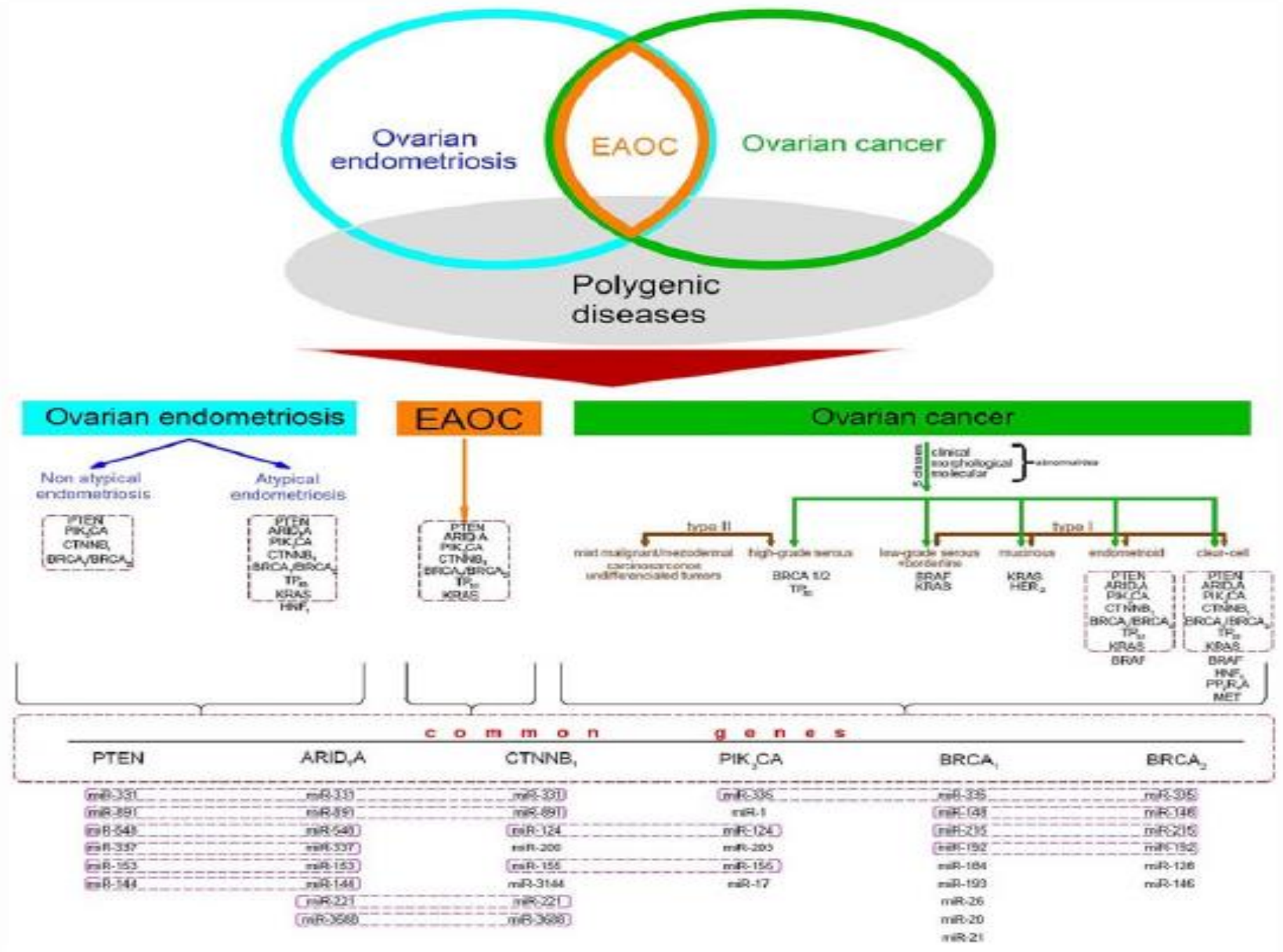
DOI: 10.1177/0300060521047701
journals.sagepub.com/home/imr
SAGE

HE4 might be a more useful tumor biomarker to detect malignancy in patients with ovarian endometrioma when malignancy is suspected

- WHEN OVARIAN MALIGNANCY IS SUSPECTED IN PATIENTS WITH **OVARIAN ENDOMETRIOSIS,** HE4 IS A MORE USEFUL TUMOR BIOMARKER TO DIAGNOSE OC WHEN ULTRASONOGRAPHY RESULTS ARE INCONCLUSIVE.

- IN PATIENTS WITH OVARIAN ENDOMETRIOSIS AND **SUSPECTED MALIGNANT ADNEXAL MASSES**, **HE4** IS A MORE USEFUL TUMORAL BIOMARKER TO DIAGNOSE OC WHEN ULTRASONOGRAPHY RESULTS ARE INCONCLUSIVE.


Ovarian endometriosis
Hyperplasia
Atypia
(transition from benign endometriosis to carcinoma)
Simple
- equal proportion of glands and stroma
Complex
-significant glandular proliferation and reduced stroma
Moderate
- simple hyperplasia
- cellular atypia
Severe
- complex hyperplasia
- more evident celluar atypia
Ovarian cancer
Endometrioid carcinoma
Clear cell carcinoma
EOAC
• coexistence of cancer cells and endometriosis in the same ovary, cancer in one ovary, endometriosis in the second ovary, ovarian cancer and pelvic endometriosis
• a similar histological pattern
• exclusion of a second malignant tumor elsewhere
• histology-proven transition from benign endometriosis to cancer


Ovarian endometriosis
EAOC
Ovarian cancer
Polygenic diseases
Ovarian endometriosis
Non atypical endometriosis
Atypical endometriosis
PTEN
PIK3CA
CTNNB1
BRCA1/BRCA2
PTEN
ARID1A
PIK3CA
CTNNB1
BRCA1/BRCA2
TP53
KRAS
HNF1
EAOC
PTEN
ARID1A
PIK3CA
CTNNB1
BRCA1/BRCA2
TP53
KRAS
Ovarian cancer
2 dualism
clinical
morphological
molecular
abnormalities
type II
type I
mixed malignant/mesodermal carcinosarcomas undifferentiated tumors
high-grade serous
BRCA1/2
TP53
low-grade serous +borderline
BRAF
KRAS
mucinous
KRAS
HER2
endometrioid
clear-cell
PTEN
ARID1A
PIK3CA
CTNNB1
BRCA1/BRCA2
TP53
KRAS
BRAF
PTEN
ARID1A
PIK3CA
CTNNB1
BRCA1/BRCA2
TP53
KRAS
BRAF
HNF1
PPP2R1A
MET
common genes
PTEN
ARID1A
CTNNB1
PIK3CA
BRCA1
BRCA2
miR-331
miR-891
miR-548
miR-337
miR-153
miR-144
miR-331
miR-891
miR-548
miR-337
miR-153
miR-144
miR-221
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miR-200
miR-155
miR-126
miR-146

Published in final edited form as:
Cancer Causes Control. 2017 May ; 28(5): 459–468. doi:10.1007/s10552-016-0841-3.

Predictors of pretreatment CA125 at ovarian cancer diagnosis: a pooled analysis in the Ovarian Cancer Association Consortium

- **Older age, history of pregnancy, history of tubal ligation, family history of breast cancer, and family history of ovarian cancer** were associated with **higher Ca125 levels** while **endometriosis** was associated with **lower ca125 levels**.

- **High BMI** and race may influence Ca125 levels independent of tumor characteristics.

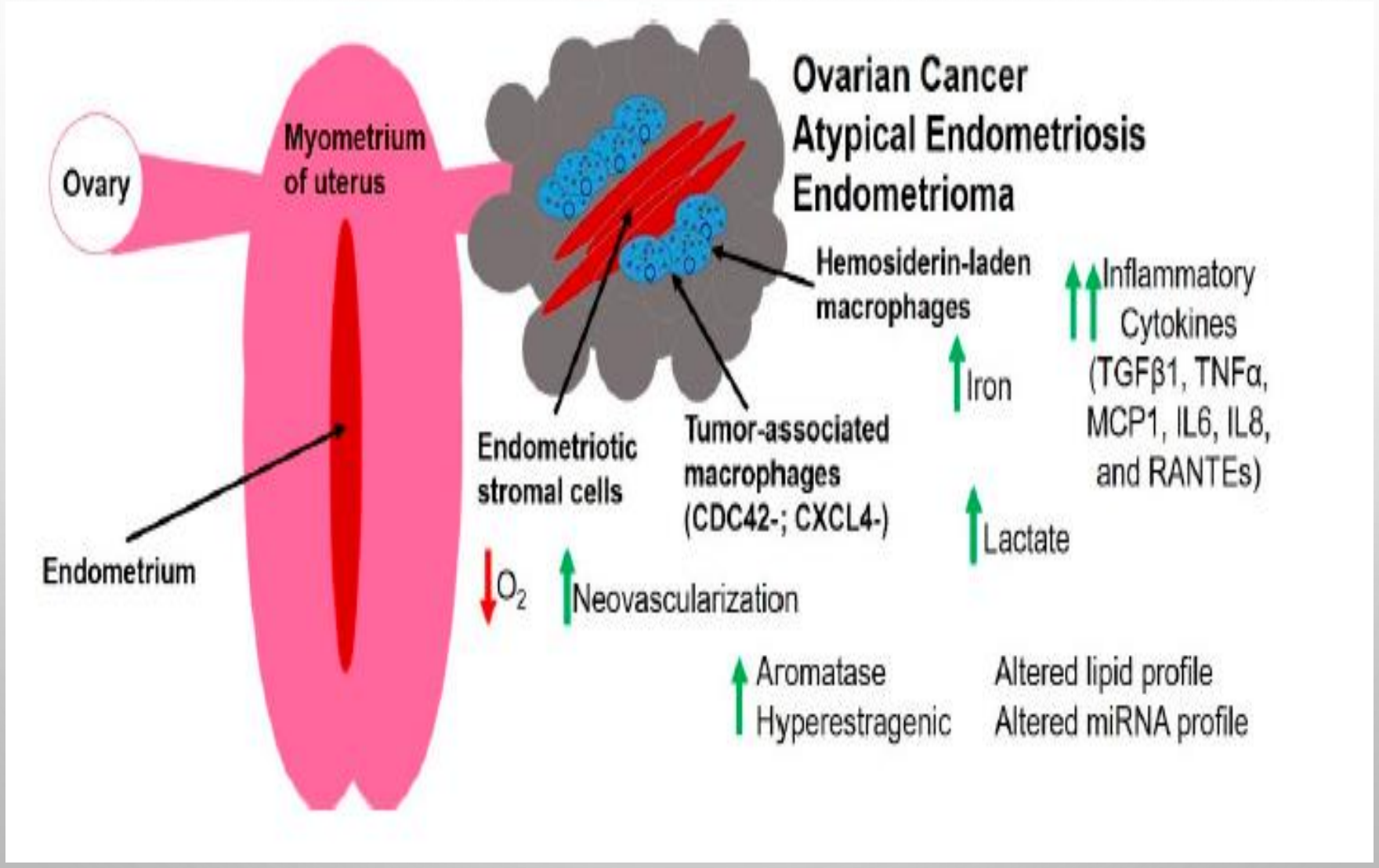
cancers

MDPI

Review

The Endometriotic Tumor Microenvironment in Ovarian Cancer

- Women with endometriosis are at increased risk of developing ovarian cancer, specifically **ovarian endometrioid, low-grade serous,** and **clear-cell adenocarcinoma.**
- Whether endometriosis-associated ovarian cancers develop from the **molecular transformation of endometriosis** or develop because of **the endometriotic tumor microenvironment remain unknown**.
- The unique tumor microenvironment of endometriosis is composed of epithelial, stromal, and immune cells, which adapt to survive in hypoxic conditions with high levels of iron, estrogen, and inflammatory cytokines and chemokines.
- Understanding the **unique molecular features of the endometriotic tumor microenvironment** may lead to impactful precision therapies and/or modalities for prevention.


Ovarian Cancer
Atypical Endometriosis
Endometrioma
Ovary
Myometrium of uterus
Endometrium
Hemosiderin-laden macrophages
Iron
Inflammatory Cytokines (TGFβ1, TNFα, MCP1, IL6, IL8, and RANTEs)
Endometriotic stromal cells
Tumor-associated macrophages (CDC42-; CXCL4-)
Lactate
O_2
Neovascularization
Aromatase
Hyperestragenic
Altered lipid profile
Altered miRNA profile

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER
OPEN ACCESS

Use of tumor markers to distinguish endometriosis-related ovarian neoplasms from ovarian endometrioma

- The assessment of serum **Ca19–9, CEA, SLX,** and **LDH levels** may be a useful tool in **the preoperative evaluation** to differentiate between endometriosis-related ovarian neoplasms and ovarian endometrioma.

- Endometriosis-related ovarian neoplasms was more likely to have **higher levels of CA19-9, CEA, SLX, and LDH** when **compared with Ca125**.

- **Ca125** levels **did not significantly differ** between the two groups.
- **Age, tumor size,** and the presence of **mural nodule** were important factors in the **preoperative prediction of endometriosis-related ovarian neoplasms.**


Thank
you!