ENDOMETRIOSIS & ADENOMYOSIS ASSOCIATION OF TURKEY 2009

Is endometriosis a pre-neoplastic condition after the age of 40 ?

Engin Oral, M.D.

Istanbul Univ. Cerrahpasa Medical Faculty

Dept. of Obstet & Gynecol

Turkish Endometriosis & Adenomyosis Association

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Conflicts of interest

- None

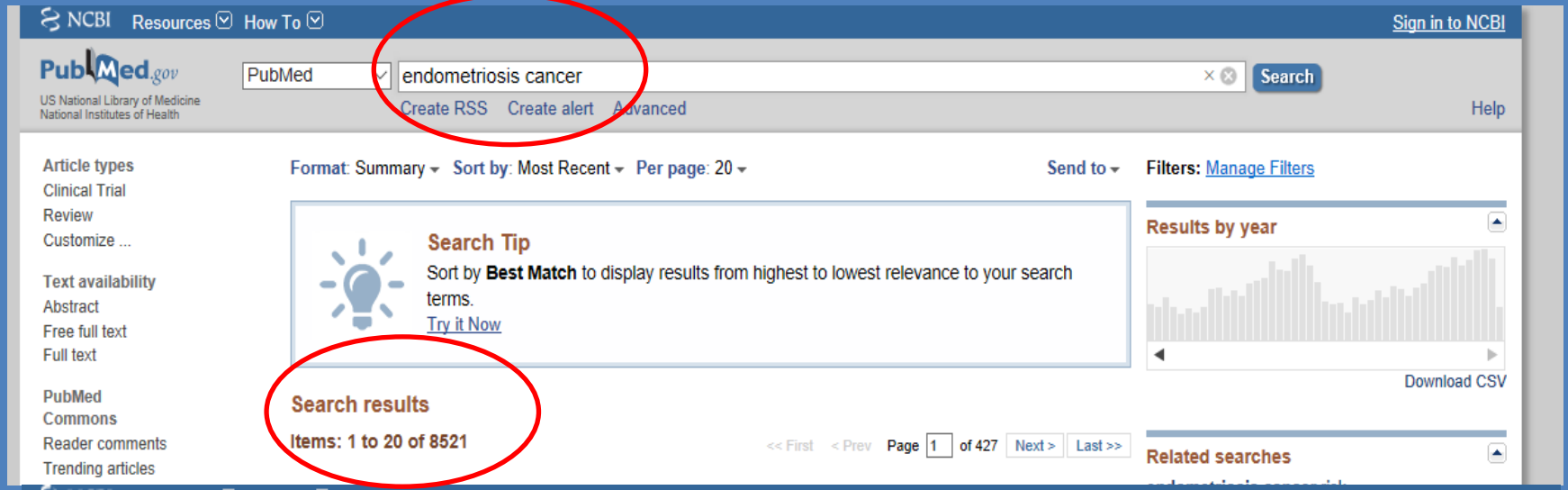
Outlines

- Overview of endometriosis and ovarian cancer
- Pathogenesis of malign transfomation of endometriosis
  - Epidemiology
  - Molecular-genetic
  - Histopathology
- Endometriosis associated non-ovarian malignancy (Endometrial, Breast)
- Adenomyosis related cancer
- Clinical Applications
- Take home messages

Questions Questions ?

- Is Endometriosis a risk factor for epithelial ovarian cancer?
- Is Endometriosis a risk factor for Borderline epithelial ovarian tumour?
- If the answers are yes, etiology?
- Which subtypes of invasive epithelial ovarian cancer are related with the endometriosis?
- What screening opportunities are available to practitioners for women with endometriosis associated ovarian cancer?
- What is the impact of the age of the patient with endometriosis on the cancer risk?
- Are there any morphologic criteria that suggest malignancy?
- What preventative measures can be offered to women with endometriosis?
- How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

14 th May, 2017
PubMed



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Arch Pathol (Chic). 1946 Mar;41:335-7.

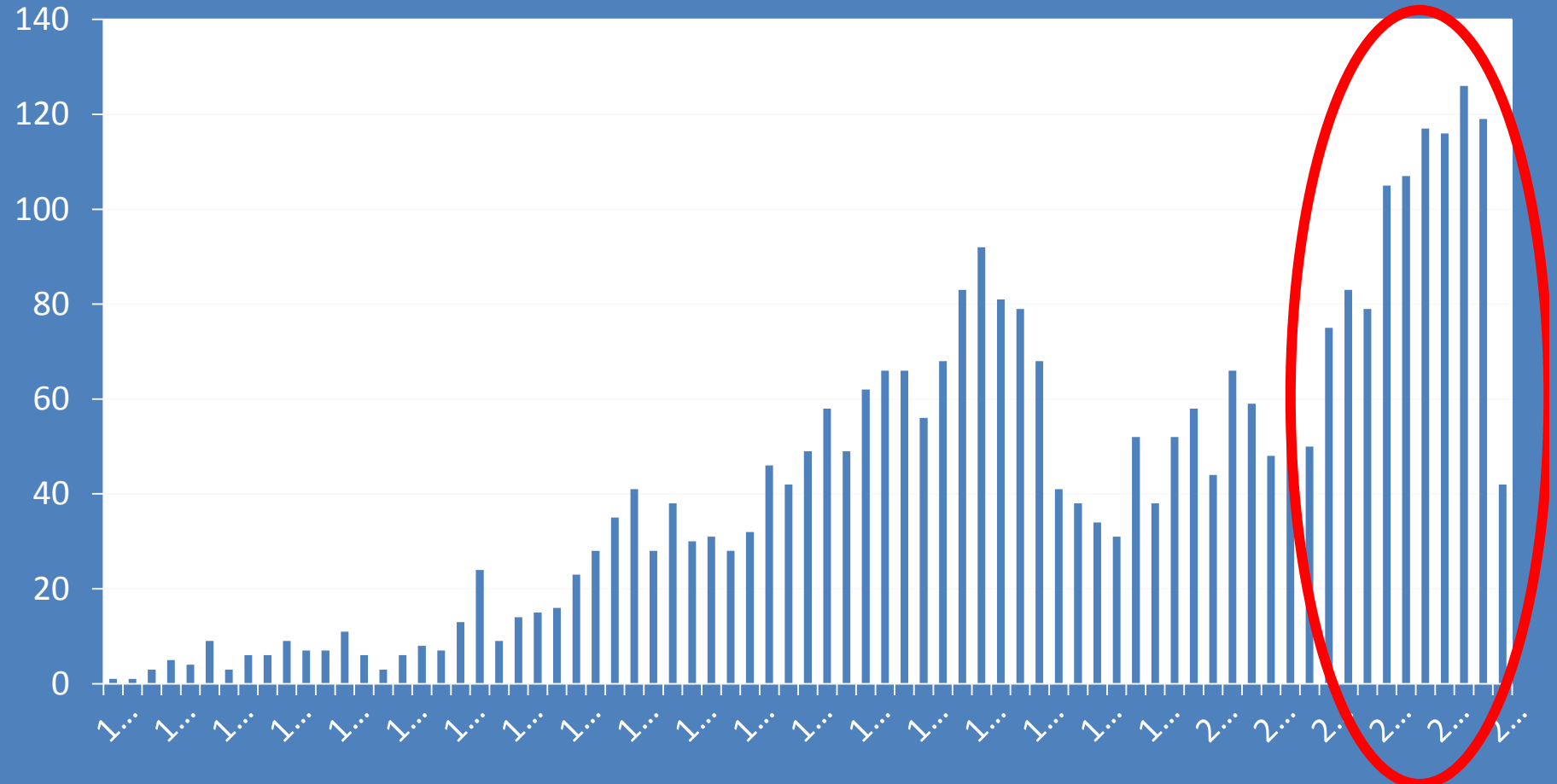
Epidermoid carcinoma arising in an endometrial cyst of the ovary.

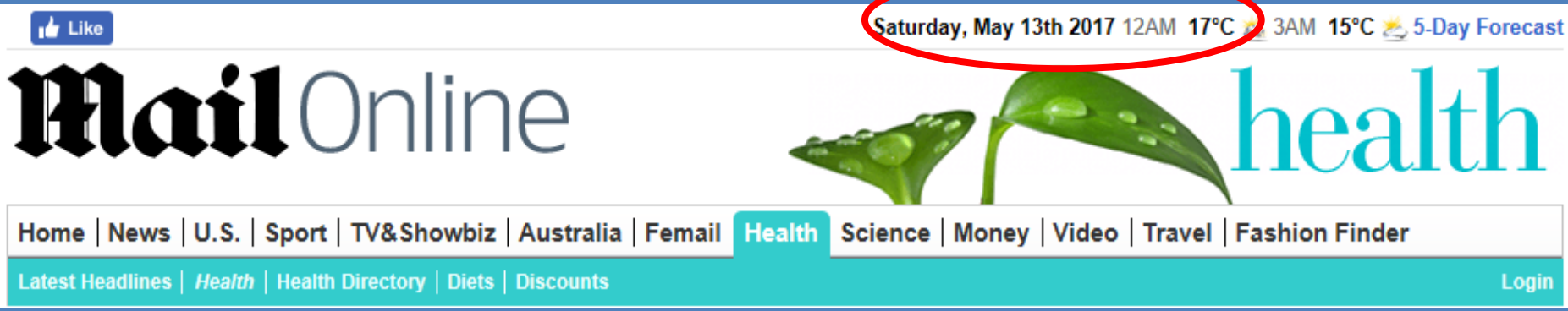
McCULLOUGH K, FROATS ER, FALK HC.

PMID: 21019996

[Indexed for MEDLINE]

PubMed Endometriosis Ovarian Cancer 1946-2017





Could common women's condition be linked to cancer? Scientists find connection between endometriosis and dangerous cell mutation

- **Experts claim to have found a link between endometriosis and mutated genes**
- **Endometriosis is a painful, incurable condition suffered by one in 10 women**
- **It affects Hollywood stars including Lena Dunham and Julianne Hough**
- **The disease is the abnormal and painful growth of tissue outside of the uterus**

By CHEYENNE ROUNDTREE FOR DAILYMAIL.COM
PUBLISHED: 21:31 BST, 11 May 2017 | **UPDATED:** 00:21 BST, 13 May 2017

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Scientists claim to have found the first link between endometriosis and gene

Researchers from BC Women's Hospital + Health Centre, BC Cancer Agency, Vancouver Coastal Health, the University of British Columbia and collaborators at Johns Hopkins Medical Institutions

Introduction

- Although it is a benign gynecologic condition, endometriosis shares pathophysiologic features with cancer.
- In recent years, both histologic and epidemiologic evidence has accumulated, suggesting that ovarian endometriosis may give rise to malignant ovarian tumors, primarily those that are epithelial in origin, known as endometriosis-associated ovarian carcinoma (EAOC) including ovarian clear cell carcinoma, endometrioid carcinoma, and the least common, seromucinous tumors.

- MOST WOMEN WİTH ENDOMETRİOSİS DO NOT DEVELOP OVARİAN CANCER

Endometriosis-Related Ovarian Neoplasms (ERONS)

- Approximately 80% of all malignancies associated with endometriosis are identified in the ovary; 20% of those are extragenital.
- Although the most common histologies are endometrioid and clear cell carcinomas, other histologies, such as carcinosarcomas and adenocarcinoma have also been reported.
- ***Endometriosis-associated ovarian cancer (EAOC)***
- Endometriosis-associated adenocarcinoma (EAC)
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Seromucinous borderline tumour,
  - Squamous cell carcinoma,
  - Carcinosarcoma,
  - Adenosarcoma,
  - Endometrioid stromal sarcoma

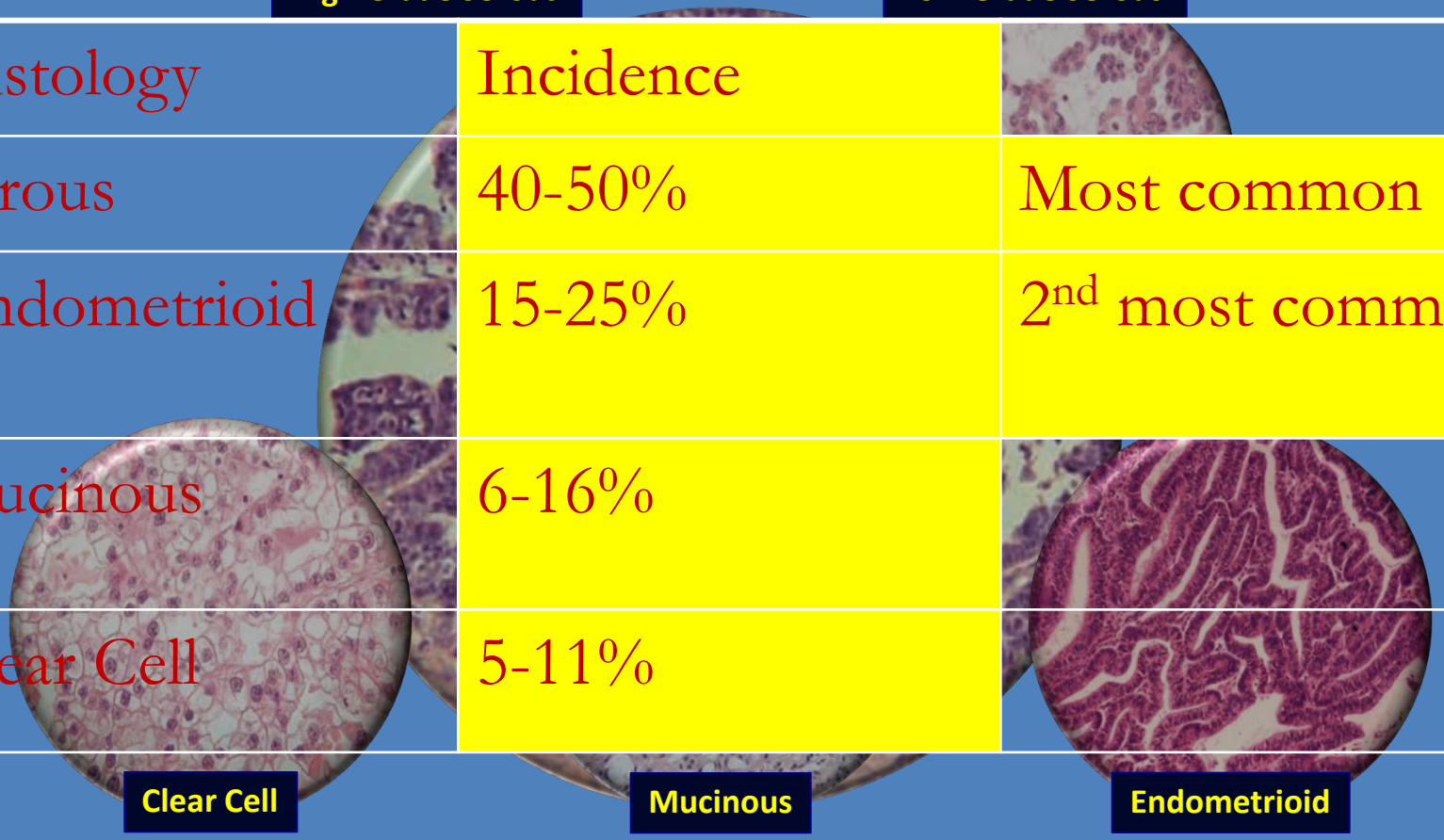
Endometriosis-Associated Ovarian Cancers (EAOC)

EAOC is defined as a neoplastic condition arising from endometriosis through clonal expansion of its constituents, including **epithelial or stromal components**.

Therefore, strictly by definition, it should be continuous with pre-existing endometriosis.

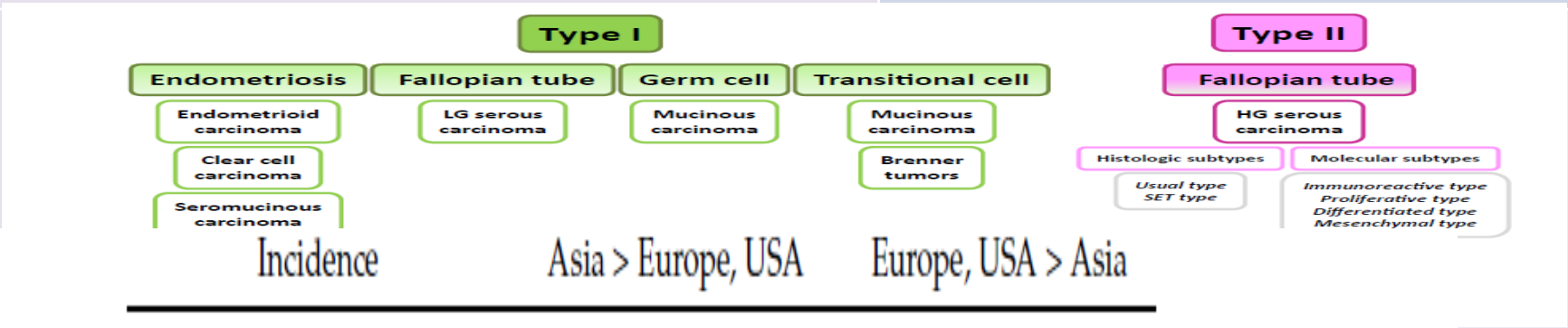
Histology and incidence of Ovarian Cancer

Histology	Incidence	
Serous	40-50%	Most common
Endometrioid	15-25%	2nd most common
Mucinous	6-16%	
Clear Cell	5-11%	



"The Dualistic Model *of ovarian carcinogenesis*"

Type I Tumors	Type II Tumors
• Low-grade, slow-growing • All histological subtypes, including serous (MPSC), endometrioid, mucinous and clear cell carcinomas • Mutations in KRAS, BRAF, ERBB2, PTEN, B-catenin, ARID1A • Benign precursors in ovary (benign and atypical proliferative (borderline) tumours and **Endometriosis ?)**	• High-grade, aggressive • **HG Serous carcinoma**, carcinosarcoma, undifferentiated carcinoma • **Mutations in TP53** • **Mutations in BRCA** • **CIN (Chromosal Instability)** • No known ovarian precursor



Ovarian Cancer-Risk

- Lifetime risk (general population): 1.4%
- BRCA 1 mutation carrier: 60 %
- BRCA 2 mutation carrier: 30%

- HNPCC (hereditary nonpolyposis colorectal carcinoma) 10%
- Endometriosis 2-3%

Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. Hum Pathol. 2005; 36:861-870
Karlan B, et al. Discussion: hereditary ovarian cancer. Gynecologic Oncology. 2003;88:S11-S3
King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;88:S11-S3
Boyd J. Specific keynote: hereditary ovarian cancer: what we know. Gynecol Oncol. 2003;88(1 Pt 2):S8-S10;discussion S11-S13

Endometriosis-associated Ovarian Cancer: A Distinct Clinical Entity?

2016

VALENTINA E. BOUNOUS[1], ANNAMARIA FERRERO[1], LUCA FUSO[1], NICOLETTA RAVARINO[2], MARCELLO CECCARONI[3], GUIDO MENATO[1] and NICOLETTA BIGLIA[1]

[1]*Unit of Gynaecology and Obstetrics, Department of Surgical Science, University of Turin, Turin, Italy;*
[2]*Department of Pathology, Mauriziano Umberto I Hospital, Turin, Italy;*
[3]*Department of Obstetrics and Gynaecology, Sacro Cuore Hospital, Negrar, Italy*

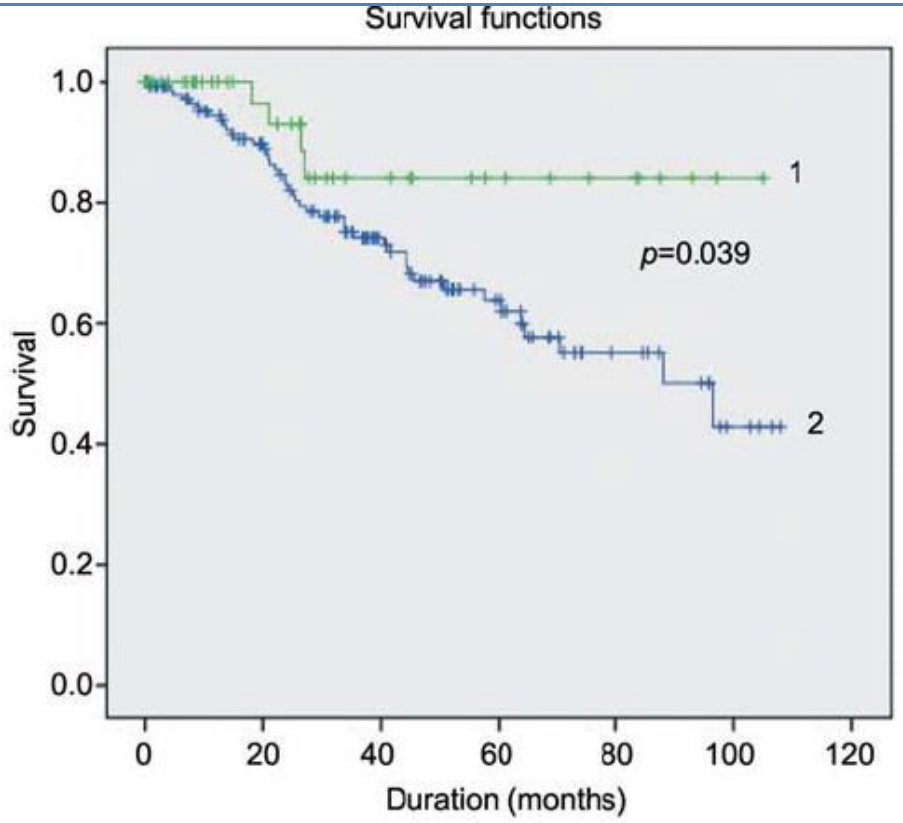


Figure 1. *Overall survival (OS) of patients with ovarian cancer ac to the presence (1) or absence (2) of associated endometriosis.*

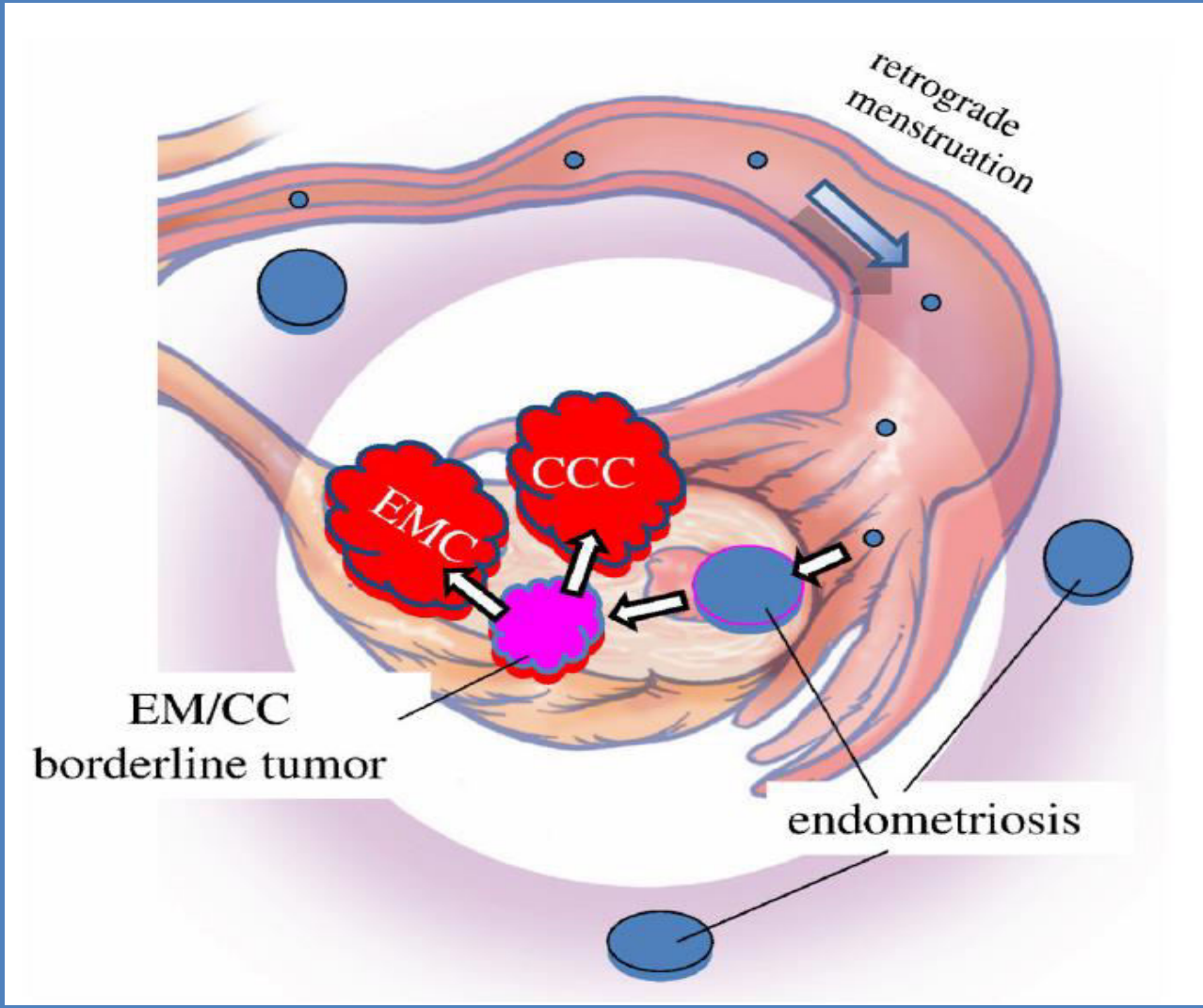
EAOC appears to be diagnosed at an earlier stage and confers a better OS. However, stratifying by stage, the advantage in survival of EAOC disappears

ANTICANCER RESEARCH *36*: 3445-3450 (2016)

Endometriosis-associated Ovarian Cancer: A Distinct Clinical Entity?

- 1) Occurrence at a younger age,
- 2) Diagnosis established at an earlier stage,
- 3) Low-grade,
- 4) Better overall survival.
- 5) predominantly endometrioid and clear-cell type

Development of low-grade endometrioid and clear cell carcinoma from endometriosis by retrograde menstruation



Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010; 34:433–443.

Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Obstetrics & Gynecology and Reproductive Biology 109 (2003) 97–101
EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY
www.elsevier.com/locate/ejogrb

2003

Prevalence of endometriosis in malignant epithelial ovary tumours

Engin Oral[a,*], Sennur Ilvan[b], Esra Tustas[a], Begum Korbeyli[a], Tugan Bese[a], Fuat Demirkiran[a], Macit Arvas[a], Derin Kosebay[a]

[a]Department of Obstetrics & Gynecology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey
[b]Department of Pathology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey

Received 15 May 2002; received in revised form 10 October 2002; accepted 28 November 2002

- A retrospective analysis of 160 malignant and 23 borderline ovarian tumours during the period 1995-2001.

Table 2
Summary of the reports on the incidence of ovarian endometriosis in ovarian cancer patients

Reference	Incidence of ovarian endometriosis (%)
Aure et al. [17]	35/831 (4.2)
Russel [18]	46/407 (11.3)
Vercellini et al. [11]	60/504 (11.9)
Jimbo et al. [19]	25/172 (14.5)
Fukunaga and Ushigome [7]	48/179 (26.8)
Ogawa et al. [8]	37/127 (29.1)
Oral et al. (2003)	14/183 (7.6)

Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies

2012

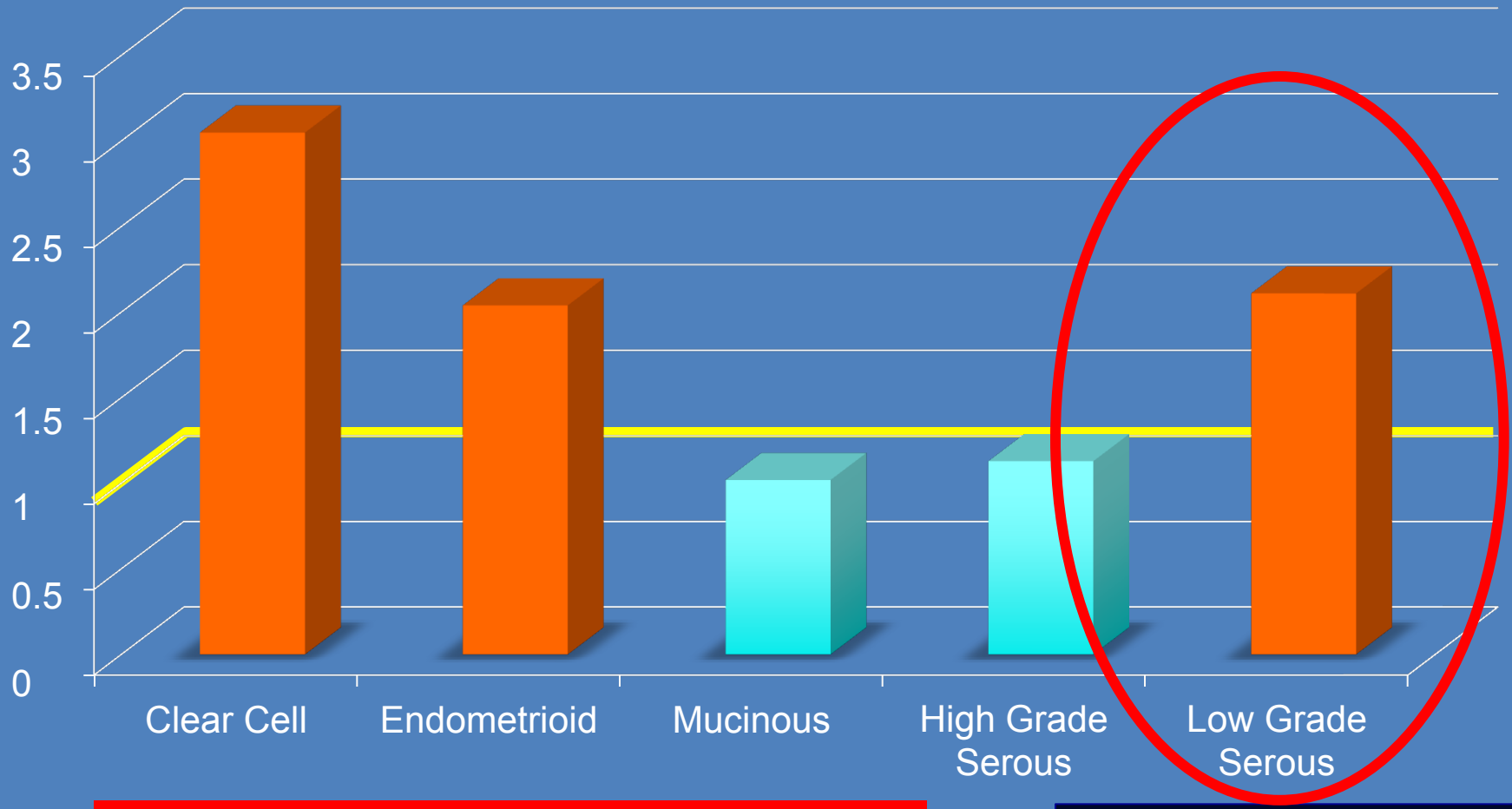
Lancet Oncol 2012; 13: 385–94

Celeste Leigh Pearce, Claire Templeman, Mary Anne Rossing, Alice Lee, Aimee M Near, Penelope M Webb, Christina M Nagle, Jennifer A Doherty, Kara L Cushing-Haugen, Kristine G Wicklund, Jenny Chang-Claude, Rebecca Hein, Galina Lurie, Lynne R Wilkens, Michael E Carney, Marc T Goodman, Kirsten Moysich, Susanne K Kjaer, Estrid Hogdall, Allan Jensen, Ellen L Goode, Brooke L Fridley, Melissa C Larson, Joellen M Schildkraut, Rachel T Palmieri, Daniel W Cramer, Kathryn L Terry, Allison F Vitonis, Linda J Titus, Argyrios Ziogas, Wendy Brewster, Hoda Anton-Culver, Alexandra Gentry-Maharaj, Susan J Ramus, A Rebecca Anderson, Doerthe Brueggmann, Peter A Fasching, Simon A Gayther, David G Huntsman, Usha Menon, Roberta B Ness, Malcolm C Pike, Harvey Risch, Anna H Wu, Andrew Berchuck, on behalf of the Ovarian Cancer Association Consortium

Ovarian Cancer Association Consortium

- Total: 23, 1444 patients
- 13,266 controls:
  - Hx of endometriosis: 818 (6.2%)
- 7,911 invasive cancer:
  - Hx of endometriosis: 738 (9.3%)
- 1,907 borderline tumors:
  - Hx of endometriosis: 168 (8.8 %)

Relationship of Endometriosis and OC



No association was noted between a history of endometriosis and borderline ovarian cancer

Pearce, Lancet Oncol (2012) 13:285

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS REVIEW ARTICLE

2013

The relation between endometriosis and ovarian cancer – a review

LENE N. HEIDEMANN[1,*], DORTHE HARTWELL[2], CHRISTIAN H. HEIDEMANN[3] & KIRSTEN M. JOCHUMSEN[1]

[1]Department of Obstetrics and Gynecology, Odense University Hospital, Odense, [2]Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, and [3]Faculty of Health Sciences, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Twenty-eight studies

The risk of ovarian cancer in women with endometriosis was reported to be a standardized incidence ratio of 1.43–8.95, a rate ratio of 1.6–2.88, an odds ratio of 1.34, with a prevalence of ovarian cancer in 2.0–17.0% of women with endometriosis.

Conversely, the prevalence of endometriosis in women with ovarian cancer ranged from 3.4 to 52.6%.

BJC

British Journal of Cancer (2014) 110, 1878–1890 | doi: 10.1038/bjc.2

Keywords: endometriosis; ovarian cancer; risk; prognosis; meta-analysis

2014

Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis

H S Kim[1], T H Kim[1], H H Chung[1] and Y S Song[*,1,2,3]

- January 1990 and December 2012, we found 20 case–control and 15 cohort studies including 444 255 patients
- Conclusions: Endometriosis is strongly associated with the increased risk of ovarian cancer, and EAOC shows favourable characteristics including early-stage disease, low-grade disease and a specific histology such as endometrioid or clear cell carcinoma. However, endometriosis may not affect disease progression after the onset of ovarian cancer.
-

Results

- **Endometriosis increases ovarian cancer risk:**
  - Case–control or two-arm cohort studies (RR, 1.265)
  - Single-arm cohort studies (SIR, 1.797)

VOLUME 34 · NUMBER 24 · AUGUST 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

2016

Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium

- Among 1.3 million women from 21 studies, 5,584 invasive epithelial ovarian cancers were identified
- (3,378 serous, 606 endometrioid, 33 mucinous, 269 clear cell, 1,000 other).

Table A4. Associations of Risk Factors With Ovarian Cancer Subtypes Based on Meta-analysis by Pooling the Results of Individual Studies in the Ovarian Cancer Cohort Consortium

Exposure	Serous	Endometrioid	Mucinous	Clear cell
Endometriosis, yes/no	1.14 (0.81 to 1.61)	2.84 (1.56 to 5.18)	5.06 (1.51 to 16.9)	3.43 (1.52 to 7.75)

Ovarian cancer in women with endometriosis

Year	Study	Association (OR, SIR, RR or HR and 95% CI)
2017	Poole et al.	1.81 (1.26-2.58) *self-reported endometriosis* 2.14 (1.45-3.15) *laparoscopically confirmed endometriosis*
2016	Wentzensen et al.	1.35 (1.07-1.71)
2016	Mogensen et al.	1.34 (1.16-1.55) *ovarian cancer* 1.64 (1.09-2.37) *endometrioid tumor* 3.64 (2.36-5.38) *clear cell tumor*
2015	Kok et al.	4.37 (1.07-17.83)
2015	Burghaus et al.	2.63 (1.28-5.41)
2014	Wang et al.	5.62 (3.46-9.14)
2014	Chang et al.	3.28 (1.37-7.85)
2013	Stewart et al.	3.11 (1.13-8.57) *nulliparous*
2013	Merritt et al.	1.92 (1.36-2.71) *for type I tumor, having a history of endometriosis*
2013	Buis et al.	8.2 (3.1-21.6)
2012	Pearce et al.	3.05 (2.43-3.84) *clear cell ovarian tumor,* 2.11 (1.39-3.20) *low-grade serous tumor,* 2.04 (1.67-2.48) *endometrioid invasive ovarian tumor* *self-reported endometriosis*
2011	Melin et al.	0.83 (0.67-1.03)
2010	Aris A.	1.6 (1.12-2.09)
2009	Moorman et al.	1.76 (1.26-2.46) *history of endometriosis*
2008	Rossing et al.	1.6 (1.1.-2.3) *among women with endometriosis and no surgery* 1.2 (0.5-2.5) *among women with endometriosis who underwent ovarian surgery*
2007	Melin et al.	1.37 (1.14-1.62)
2007	Kobayashi et al.	8.95 (4.12-15.3) *ovarian endometrioma cohort*

Human Reproduction, Vol.28, No.12 pp. 3358–3369, 2013
Advanced Access publication on September 5, 2013 doi:10.1093/humrep/det340

2013

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Increased risk for ovarian cancer and borderline ovarian tumours in subfertile women with endometriosis

C.C.M. Buis[1], F.E. van Leeuwen[2], T.M. Mooij[2], and C.W. Burger[1,*] on behalf of the OMEGA Project Group[†]

[1]Department of Obstetrics and Gynaecology, Division of Gynaecologic Oncology, Erasmus Medical Center Rotterdam, PO Box 2040, Rotterdam 3000 CA, The Netherlands [2]Department of Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, The Netherlands

*Correspondence address. Tel: +31 10 4633617; E-mail: c.w.burger@erasmusmc.nl

.

1980-1995

. 3657 Endometriosis

. 5247 Control subfertile women

(male factor or idiopathic) without endometriosis

Table II Risk of ovarian tumours associated with endometriosis.

	All cases (n = 34)		Ovarian cancer (n = 19)		BOT (n = 15)	
	HR	95% CI	HR	95% CI	HR	95% CI
Ovarian endometriosis[d]	11.3	4.0–31.8	15.0	3.1–72.4	8.9	2.2–35.7

Endometriosis –Borderline ovarian tumours

Table 5. **Prevalence of endometriosis in women with borderline ovarian tumours**

Bell&Scully, 1985[41]	15% (3/20)
Rutgers&Scully, 1988[42]	53% (19/36 müllerian-type BOT)
Snyder RR et al., 1988[43]	52% (16/31 endometrioid BOT)
Fukunaga M et al., 1997[36]	9.5% (4/42)
Bell&Kurman, 2000[44]	42% (14/33 endometrioid BOT)
Oral E et al., 2003[15]	13% (3/23)
Roth LM et al., 2003[45]	63% (19/30 endometrioid BOT)
Zhao C et al., 2011[39]	34% (14/41 clear cell BOT)
Pearce CL et al., 2012[19]	8.8% (168/1907)
Uzan C et al., 2012[46]	19% (3/16 endometrioid BOT)

Oral et al., 2016

Oral et al.. 2016, submitted Cerrahpaşa Medical Faculty, Istanbul

- During the years 1995-2011, a total of 661 women with ovarian tumours (530 malignant ovarian cancer and 131 borderline ovarian tumours) were retrospectively analyzed
- Endometriosis was found in 48 of 661 cases (7.3%).
- The prevalence of ovarian endometriosis coexistence in borderline tumors (16/131, 12%) was found to be significantly higher than that in malignant ovarian tumours (32/530, 6%; *p=0.02*).
- Infertility was noted in nearly half of patients with endometriosis-associated BOT and 1/3 of patients with endometriosis-associated malignant ovarian tumours

Cancer Causes Control (2017) 28:393–403
DOI 10.1007/s10552-016-0848-9

CrossMark

ORIGINAL PAPER

2017

Hormonal and reproductive factors and the risk of ovarian cancer

Anita Koushik[1,2] · Anne Grundy[1,2] · Michal Abrahamowicz[3,4] · Jocelyne Arseneau[5,6] · Lucy Gilbert[6] · Walter H. Gotlieb[7] · Julie Lacaille[1] · Anne-Marie Mes-Masson[1,8] · Marie-Élise Parent[1,2,9] · Diane M. Provencher[1,10] · Lesley Richardson[1] · Jack Siemiatycki[1,2]

A population-based case–control study was carried out in Montreal, Canada from 2011 to 2016, including 496 cases and 908 controls

Table 2 Multivariable ORs (95% CIs) of epithelial ovarian cancer associated with hormonal and reproductive characteristics

	Controls ($n=908$) n (%)	Cases ($n=496$) n (%)	OR[a] (95% CI)
Endometriosis[b]			
Never	843 (94.4)	441 (90.7)	1.00 (ref)
Ever	50 (5.6)	45 (9.3)	1.65 (1.08–2.54)

Table 3 Multivariable ORs (95% CIs) of invasive ovarian cancer and borderline ovarian cancer associated with

	Controls ($n=908$)	Invasive ($n=364$)		Borderline ($n=132$)		p_{het}[b]
	n (%)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)	
Endometriosis[c]						
Never	843 (94.4)	324 (90.5)	1.00 (ref)	117 (91.4)	1.00 (ref)	0.81
Ever	50 (5.6)	34 (9.5)	1.70 (1.07–2.71)	11 (8.6)	1.55 (0.77–3.13)	

Table 4 Multivariable ORs (95% CIs) of Type I and Type II ovarian cancer associated with hormonal and reproductive characteristics

	Controls ($n=908$)	Type I ($n=103$)		Type II ($n=261$)		p_{het}[b]
	n (%)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)	
Endometriosis[c]						
Never	843 (94.4)	85 (85.0)	1.00 (ref)	239 (92.6)	1.00 (ref)	0.04
Ever	50 (5.6)	15 (15.0)	2.96 (1.54–5.67)	19 (7.4)	1.33 (0.76–2.32)	

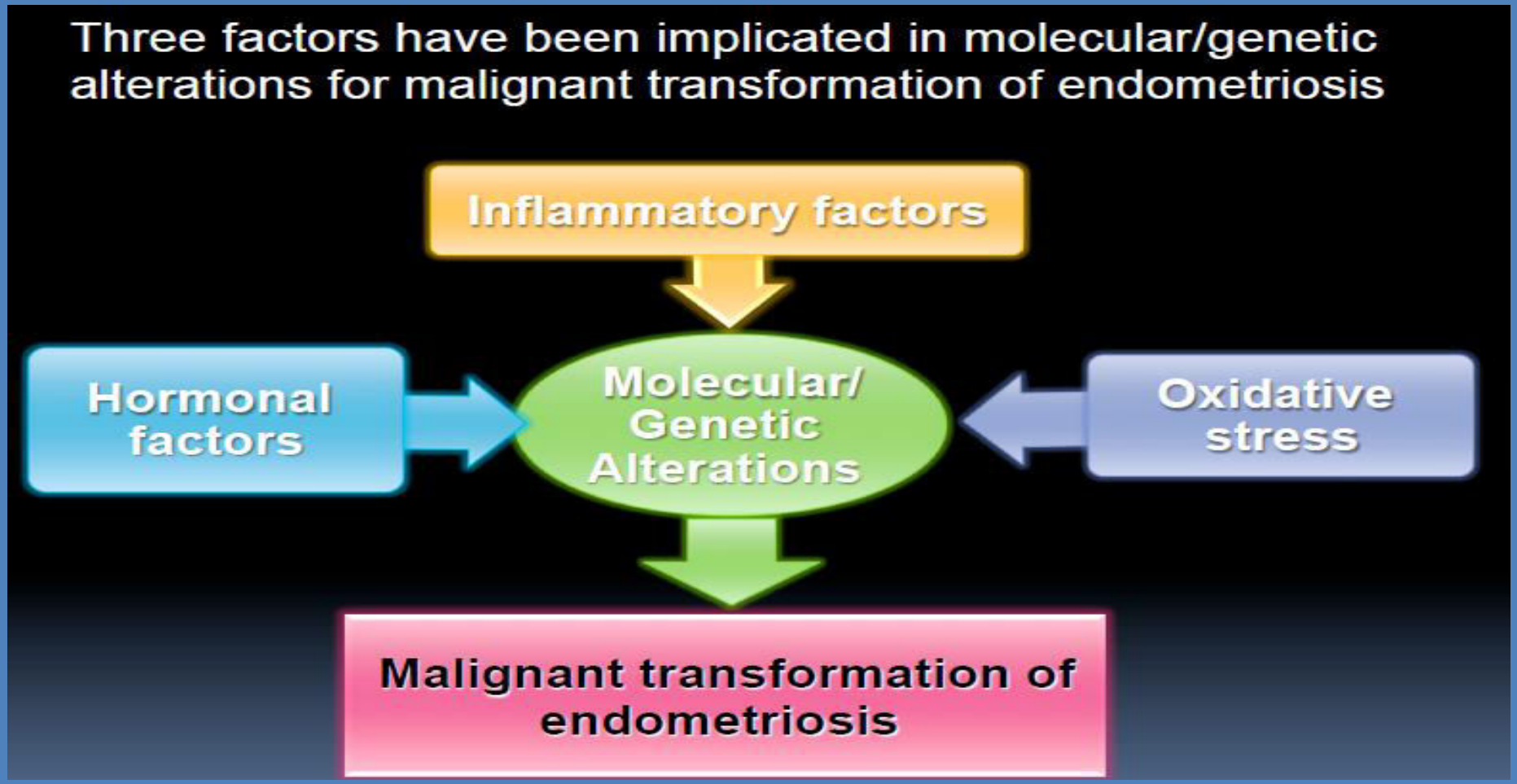
A history of endometriosis was most strongly associated with Type I cancers

ENDOMETRIOSIS AND ENDOMETRIOSIS ASSOCIATED OVARIAN MALIGNACY PREVALANCE IN 40 AGES AND OLDER WOMEN OPERATED DUE TO ADNEXAL MASS

- Of the 1156 subjects who participated in this study, 319 (27.6%) were diagnosed as having endometriosis. Among these patients 21 (6.6%) were diagnosed as having malign disease which was developed from basis of the endometriosis
- Endometrioid adenocarcinoma was the most frequently encountered histological subtype, accounting for the 5 of the 21 tumours (23.8%), followed by mixed (clear cell and endometriod) 4 (19%), clear cell 3 (14.3%), mucinous borderline tumours 3 (14.3%), endometriod borderline tumours 2 (9.5%) and others 4 (19%).

PS01-108 ENDOMETRIOSIS AND ENDOMETRIOSIS ASSOCIATED OVARIAN MALIGNACY PREVALANCE IN 40 AGES AND OLDER WOMEN OPERATED DUE TO ADNEXAL MASS Engin Oral (TR)

Potential Different Mechanisms Involved In The Malignant Transformation Of Endometriotic Lesions



Endometriosis-associated ovarian cancer Pathogenesis

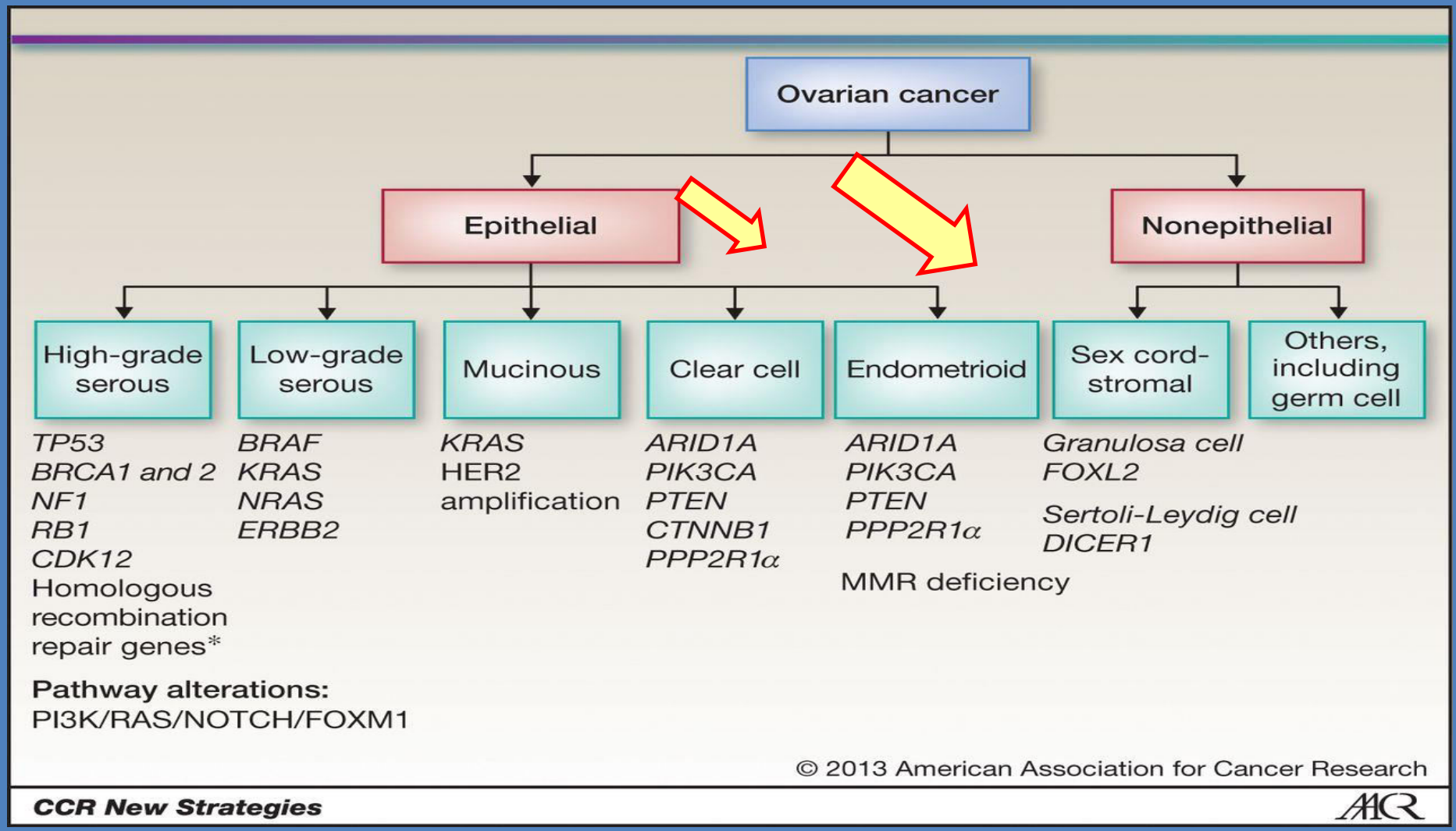
- Inflammation
- Heme and free iron are pro oxidant
  - Induce oxidative stress
  - DNA damage results
  - Increased numbers of cytokines and growth factors
  - Inflammation is hallmark of endometriosis
    - Endometriotic implant →Production of proinflammatory cytokines →Persistent exposure to these factors →disruption of homeostasis, genomic instability →abnormal proliferation
    - Microenvironment of endometriotic cysts (↑free iron, ↑ lipid peroxidase) induces state of oxidative stress that plays a role in malignant transformation of endometriosis

Endometriosis-associated ovarian cancer Pathogenesis

- Hormonal factors
- Steroid Hormones
  - Estrogen may increase risk of malignant transformation
  - High levels of aromatase activity found
  - ↑estrogen persist due to aromatase activity in microenvironment of endometriotic implant and in the ovary →alters physiologic milieu around ovarian surface→ proliferation with increased chance of DNA damage and mutations.

Proposed Genetic Mechanisms Of Malignant Transformation

Prevalence Of Histologic Types Of Epithelial Ovarian Cancer And Their Associated Molecular Genetic Changes



Banerjee S , and Kaye S B Clin Cancer Res 2013

Endometrioid carcinoma

- Approximately 15%-20% of patients have synchronous endometrioid endometrial carcinoma.
- Mutations;
  - PTEN (20%),
  - CTTNB1 (beta- catenin; 16%-54%),
  - KRAS (4%-5%),
  - PIK3CA (20%),
  - ARID1A (AT-rich interactive domain 1A; 30%)

Kurman RJ, Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancereshifting the paradigm. Hum Pathol 2011; 42: 918e31.

Clear cell carcinoma

- Loss of heterogeneity (LOH) of PTEN (20%),
- Mutation of KRAS (5%-16%),
- PIK3CA (50%),
- TGF-bII (66%),
- ARID1A (46%-57%)

SEMINAL CONTRIBUTION

Evidence of a genetic link between endometriosis and ovarian cancer

2016

Alice W. Lee, M.P.H.,[a] Claire Templeman, M.D.,[b] Douglas A. Stram, B.S.,[a] Jonathan Beesley, Ph.D.,[c] Jonathan Tyrer, Ph.D.,[d] Andrew Berchuck, M.D.,[e] Paul P. Pharoah, Ph.D.,[d,f] Georgia Chenevix-Trench, Ph.D.,[c] and Celeste Leigh Pearce, Ph.D.,[a,g] on behalf of the Ovarian Cancer Association Consortium

Objective: To evaluate whether endometriosis-associated genetic variation affects risk of ovarian cancer.
Design: Pooled genetic analysis.
Setting: University hospital.
Patient(s): Genetic data from 46,176 participants (15,361 ovarian cancer cases and 30,815 controls) from 41 ovarian cancer studies.
Intervention(s): None.
Main Outcome Measure(s): Endometriosis-associated genetic variation and ovarian cancer.
Result(s): There was significant evidence of an association between endometriosis-related genetic variation and ovarian cancer risk, especially for the high-grade serous and clear cell histotypes. Overall we observed 15 significant burden statistics, which was three times more than expected.

single nucleotide polymorphisms (SNPs), which are both common in these two diseases

Gynecologic Oncology 145 (2017) 142–147

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journal homepage: www.elsevier.com/locate/ygyno

2017

Genetic risk factors for ovarian cancer and their role for endometriosis risk

Stefanie Burghaus [a], Peter A. Fasching [a,b,*], Lothar Häberle [c], Matthias Rübner [a], Kathrin Büchner [a], Simon Blum [a], Anne Engel [c], Arif B. Ekici [d], Arndt Hartmann [e], Alexander Hein [a], Matthias W. Beckmann [a], Stefan P. Renner [a]

Table 4

12 validated OCAC SNPs. Odds ratios (ORs) with 95% confidence intervals (CIs) (in brackets) and corresponding P values are shown.

SNP	Gene	Unadjusted analysis			Analysis adjusted for clinical predictors		
		OR (CI)[a]	Unorrected *P* value[b]	Corrected *P* value[c]	OR (CI)[d]	Uncorrected *P* value[b]	Corrected *P* value[c]
rs2072590	*HAGLROS,HAGLR*	0.99 (0.80–1.22)	0.94	1.00	0.98 (0.75–1.27)	0.85	1.00
rs2665390	*TIPARP*	0.87 (0.60–1.27)	0.46	1.00	0.91 (0.56–1.47)	0.70	1.00
rs10069690	*TERT*	1.32 (1.06–1.63)	0.01	0.15	1.22 (0.94–1.59)	0.14	1.00
rs11782652	*CHMP4C*	0.93 (0.62–1.39)	0.72	1.00	0.76 (0.46–1.28)	0.31	1.00
rs10088218	*LINC00824*	1.01 (0.75–1.34)	0.97	1.00	1.08 (0.75–1.55)	0.67	1.00
rs1243180	*MLLT10*	1.02 (0.83–1.24)	0.87	1.00	0.96 (0.75–1.24)	0.76	1.00
rs7405776	*HNF1B*	0.96 (0.78–1.17)	0.65	1.00	0.72 (0.56–0.94)	0.01	0.15
rs757210	*HNF1B*	0.93 (0.76–1.13)	0.45	1.00	0.73 (0.56–0.94)	0.02	0.16
rs11651755	*HNF1B*	0.84 (0.69–1.02)	0.08	0.86	0.66 (0.51–0.84)	<0.01	0.01
rs9303542	*SKAP1*	1.19 (0.95–1.48)	0.13	1.00	1.03 (0.78–1.35)	0.86	1.00
rs8170	*BABAM1*	0.80 (0.62–1.03)	0.09	0.90	0.76 (0.55–1.06)	0.10	0.93
rs2363956	*ANKLE1*	0.97 (0.80–1.17)	0.75	1.00	0.98 (0.77–1.24)	0.86	1.00

[a] OR calculated with simple logistic regression model, one SNP per model.

[b] *P* value, uncorrected for multiple testing.

[c] *P* value, corrected for multiple testing (Bonferroni-Holm).

[d] OR calculated with multiple logistic regression model.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N ENGL J MED 376;19 NEJM.ORG MAY 11, 2017

Cancer-Associated Mutations in Endometriosis without Cancer

M.S. Anglesio, N. Papadopoulos, A. Ayhan, T.M. Nazeran, M. Noë, H.M. Horlings, A. Lum, S. Jones, J. Senz, T. Seckin, J. Ho, R.-C. Wu, V. Lac, H. Ogawa, B. Tessier-Cloutier, R. Alhassan, A. Wang, Y. Wang, J.D. Cohen, F. Wong, A. Hasanovic, N. Orr, M. Zhang, M. Popoli, W. McMahon, L.D. Wood, A. Mattox, C. Allaire, J. Segars, C. Williams, C. Tomasetti, N. Boyd, K.W. Kinzler, C.B. Gilks, L. Diaz, T.-L. Wang, B. Vogelstein, P.J. Yong, D.G. Huntsman, and I.-M. Shih

2017

- The **exomesequencing study** on samples from **deep infiltrating endometriosis lesions** provides interesting results and shows further complexity of the disorder. They identified **somatic mutations in lesions from 19 of 24 patients (79%).** The number of mutations in each lesion was variable. Lesions **from 5 patients (21%) harbored known somatic cancer driver mutations in ARID1A, PIK3CA, KRAS, and PPP2R1A.** More detailed experiments on samples from **3 other patients revealed KRAS mutations in 2 of them.** One patient had two different activating KRAS mutations, and the other patient had the same somatic KRAS mutation in three separate lesions. Lesions contain multiple cell types, and KRAS mutations were detected only in the epithelium and not in the stroma.

- The potential association between **endometriosis and cancer** has been theorized for decades.
- The establishment of an association was reported **90 years ago** ***(Sampson 1925)*** and was refined in 1953, proposing that benign endometriosis should be observed in close anatomic proximity to the arising endometriosis-associated cancer***(Scott 1953).***

Definition of neoplastic transformation of endometriosis

Based on the criteria by Sampson and Scott, neoplastic transformation of endometriosis is defined as follows:

- 1) adjacent to unequivocal foci of endometriosis;
- 2) absence of any other primary tumour;
- 3) microscopic features are within a spectrum of well-recognized neoplasms originating from endometriosis;
- 4) a transition from neoplastic epithelium (or stromal component) to endometriosis.

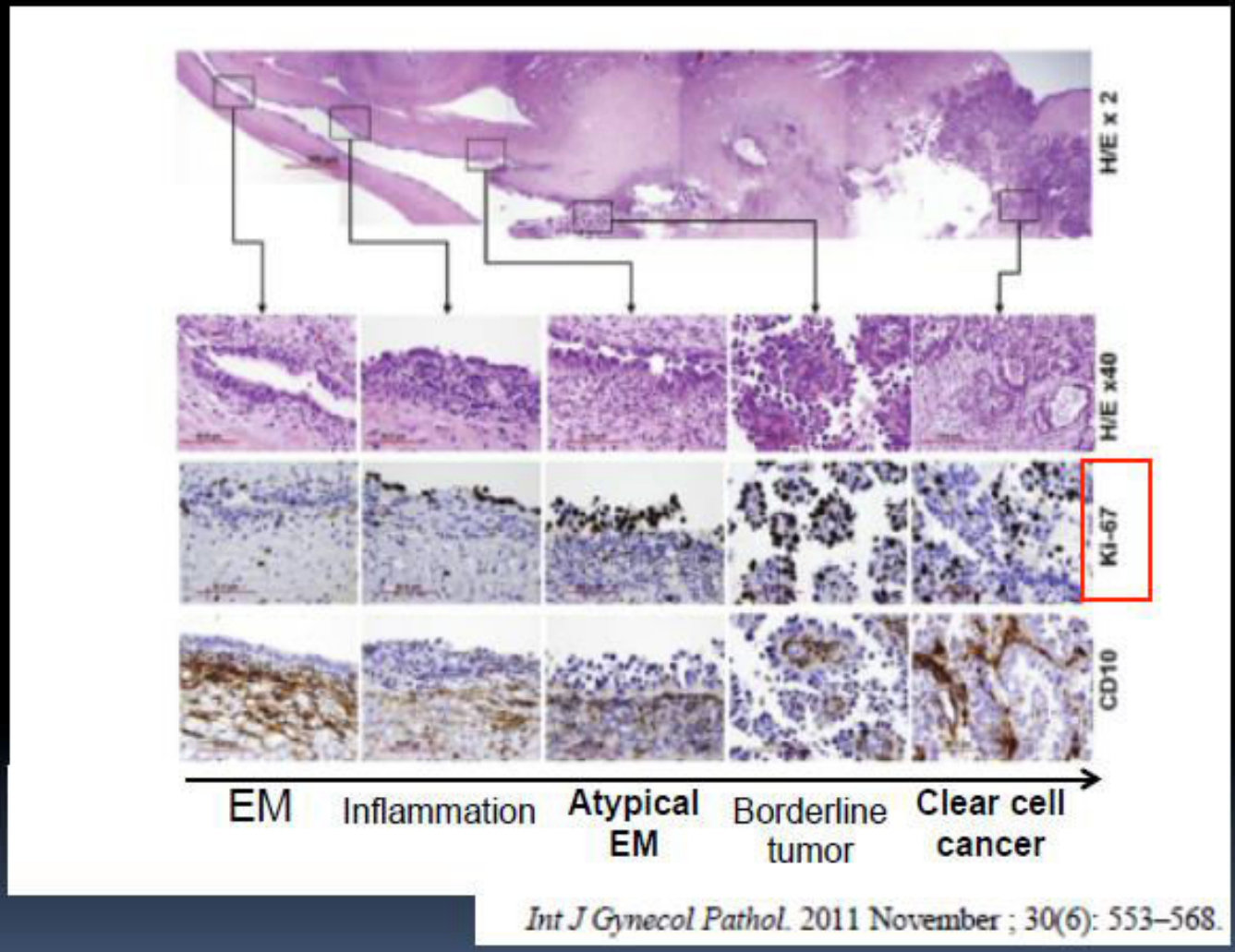
Sampson JA. Endometrial carcinoma of the ovary, arising in endo- metrial tissue in that organ. Arch Surg 1925; 10: 1e72.

Scott RB. Malignant changes in endometriosis. Obstet Gynecol 1953

Endometriosis and Cancer: Hypotheses

1. Endometriotic implants may directly undergo malignant transformation, perhaps through an atypical transition phase
2. Endometriosis and cancer share common antecedent mechanisms and/or predisposing factors (genetic susceptibility, immune/ angiogenic dysregulation, environmental toxin exposure).

Morphologic steps of tumor progression from endometriosis to endometriosis-associated carcinoma



Int J Gynecol Pathol. 2011 November ; 30(6): 553–568.

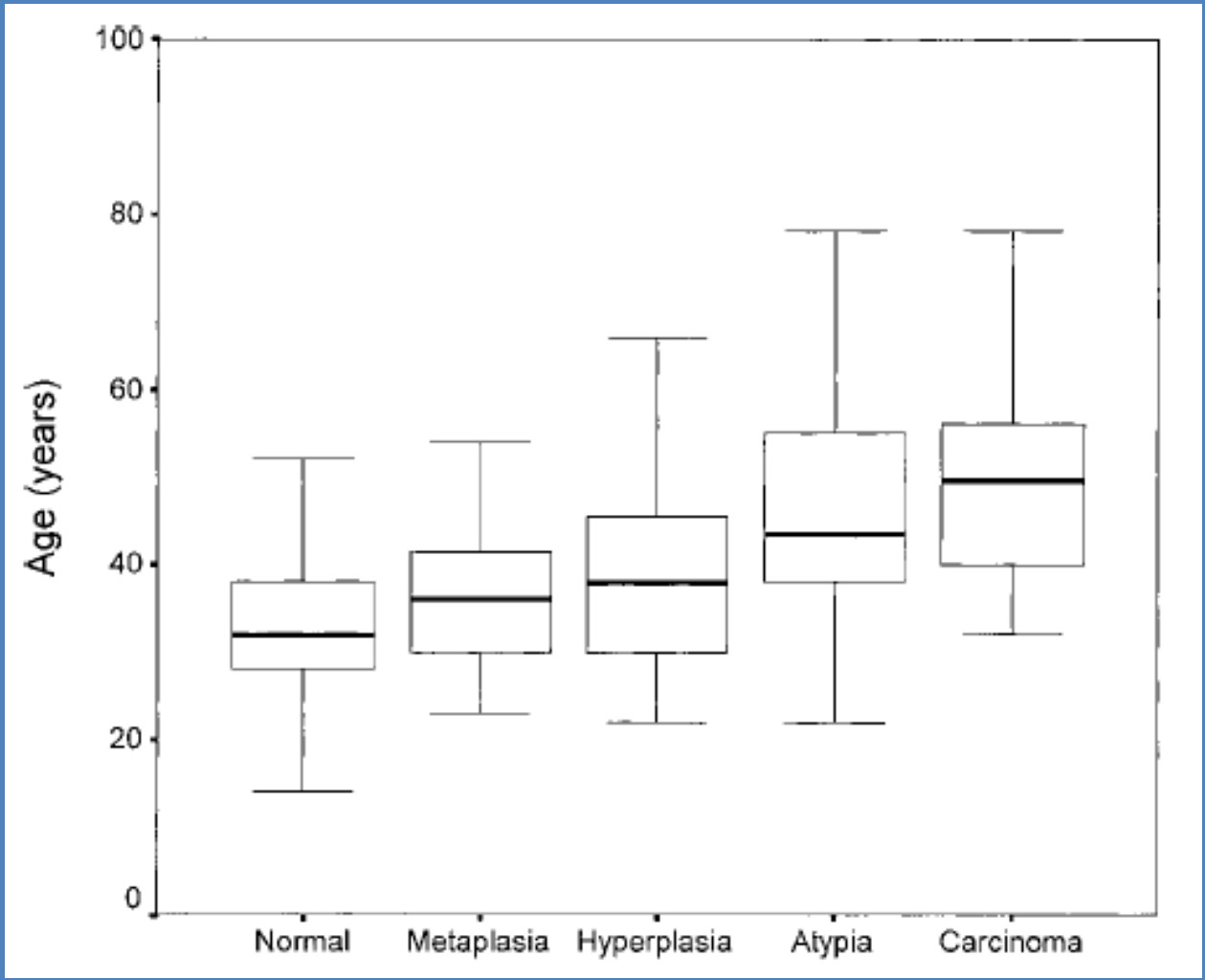
Endometriosis → Atypical Endometriosis → Borderline Tumors → Endometriosis-Associated OVCA

Atypical endometriosis

- ~8% of endometrioses contain atypical endometriosis.
- In ovarian cancer, atypical endometriosis is present in 23% of endometrioid carcinomas and in 36% of clear cell carcinomas (Fukunaga et al. *Histopathology* 1997) .
- Most atypical endometriosis show direct continuity with endometriotic-associated carcinoma, but are rarely seen in noncancer endometriosis .
- Women with previously biopsy-proven atypia within endometriosis were found to develop a EAOC in the same ovary some years later
- The spatial and chronological association with endometriosis-associated carcinoma suggest that atypical endometrioses are precancerous lesions, as seen in atypical hyperplasia of the endometrium (Prefumo et al. *Gynecol Oncol* 2002).

Epithelial abnormalities in cystic ovarian endometriosis (n:339)

2002



A statistically significant trend for increasing age from normal epithelium to carcinoma was observed ($P < 0.001$).

*Prefumo et al. Gynecologic Oncology 84, 280–284 (2002

Delineating Which Patients May be at an Increased Risk for Ovarian Cancer

Women with long-standing history of endometriosis.
Endometriosis diagnosed at an early age.
Endometriosis associated infertility and/or history of infertility treatment.
Patients with Ovarian endometrioma.

Nezhat F. et al.Malignant transformation of endometriosis. Fertil Steril 2014.

AOGS SYSTEMATIC REVIEW

Risk factors of epithelial ovarian carcinomas among women with endometriosis: a systematic review

2016

LINE H. THOMSEN[1], TINE H. SCHNACK[2], KRISTINA BUCHARDI[3], LONE HUMMELSHOJ[4], STACEY A. MISSMER[5,6], AXEL FORMAN[1] & JAN BLAAKAER[1]

- A lower risk of epithelial ovarian cancer was observed in women with documented complete surgical excision of endometriotic tissue and suggested among women with unilateral oophorectomy.
- The use of oral contraceptives (≥10 years) may be associated with a lower risk of epithelial ovarian cancer among women with endometriosis,
- whereas older age at endometriosis diagnosis (≥45 years, pre- or postmenopausal), nulliparity, hyperestrogenism (endogenous or exogenous), post menopausal status at endometriosis diagnosis, solid compartments as well as larger size of endometrioma (≥9 cm in diameter at endometriosis diagnosis) were all associated with an increased risk of ovarian cancer.

Development of ovarian cancer after excision of endometrioma

2016

Hirofumi Haraguchi, M.D., Kaori Koga, M.D., Ph.D., Masashi Takamura, M.D., Ph.D., Tomoko Makabe, M.D., Fusako Sue, M.D., Mariko Miyashita, M.D., Yoko Urata, M.D., Ph.D., Gentaro Izumi, M.D., Ph.D., Miyuki Harada, M.D., Ph.D., Tetsuya Hirata, M.D., Ph.D., Yasushi Hirota, M.D., Ph.D., Osamu Wada-Hiraike, M.D., Ph.D., Katsutoshi Oda, M.D., Ph.D., Kei Kawana, M.D., Ph.D., Tomoyuki Fujii, M.D., Ph.D., and Yutaka Osuga, M.D., Ph.D.

Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

Objective: To determine the prevalence rate of subsequent development of ovarian cancer after excision of endometrioma.
Design: Retrospective cross-sectional study.
Setting: University hospital.
Patient(S): A total of 485 women with endometrioma.
Intervention(s): Excisions of endometrioma were performed between 1995 and 2004. Data were collected from medical records in 2013.
Main Outcome Measure(s): Age, revised American Society for Reproductive Medicine score, cyst diameter, follow-up periods, endometrioma recurrence, and development of ovarian cancer.
Result(s): Recurrence of endometrioma was recorded in 121 patients (24.9% of the entire cohort), and 4 patients (0.8% of the entire cohort) developed ovarian cancer. All ovarian cancers developed from a recurrent endometrioma (3.3% of patients who experienced recurrence). Recurrence of endometrioma was significantly associated with ovarian cancer development.
Conclusion(s): Ovarian cancers can develop after excision of endometrioma and are more likely to arise from recurrent endometrioma. Special care such as rigorous follow-up should be practiced to manage patients who experience recurrence of endometrioma. (Fertil Steril® 2016;106:1432–7. ©2016 by American Society for Reproductive Medicine.)

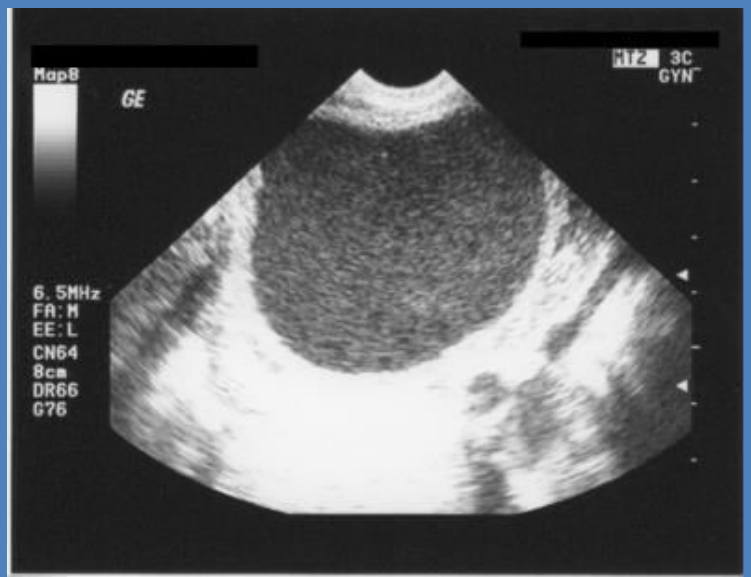
What Diagnostic Opportunities are Available to Practitioners for Women with Endometriosis?

Pelvic US

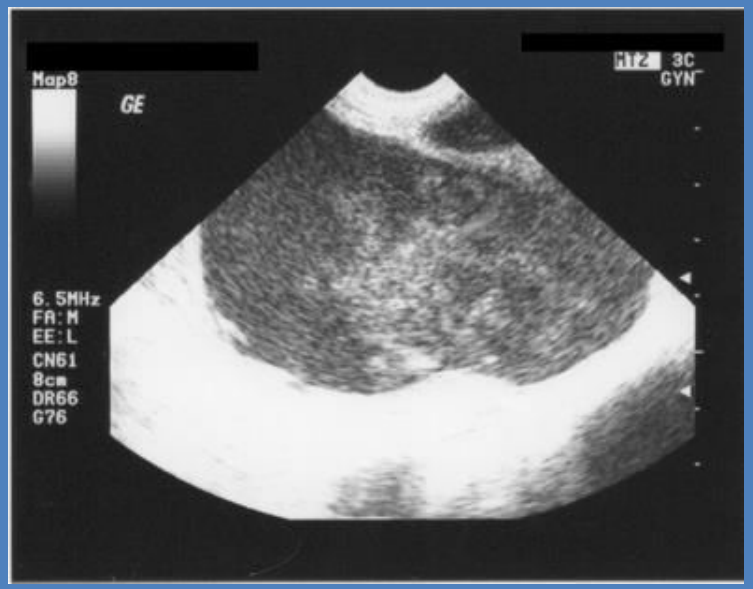
- useful in the identification of ovarian endometrioma with homogeneous hypoechogenic cystic features and those with mural malignant changes
- hyperdense mural nodules within the ovary and rapid growth of an endometrioma can be visualized on MRI – associated with malignant transformation

- difficult to detect relatively small endocystic echogenic components with this modality

Endometrioma with diffuse, homogenous hypoechogenic features



Endometrioma with mural malignant features



USG

Ultrasound Obstet Gynecol 2011; 38: 99–106

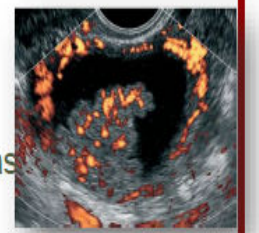
Ovarian cancer arising in endometrioid cysts: ultrasound findings

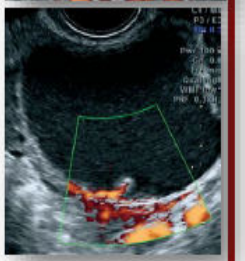
A. C. TESTA*, D. TIMMERMAN†, C. VAN HOLSBEKE‡, G. F. ZANNONI§, S. FRANSIS¶, P. MOERMAN**, V. VELLONE§, F. MASCILINI*, A. LICAMELI*, M. LUDOVISI*, A. DI LEGGE*, G. SCAMBIA* and G. FERRANDINA††

ultrasound features for characterising benign from malignant masses remain valid

"endometrioma"

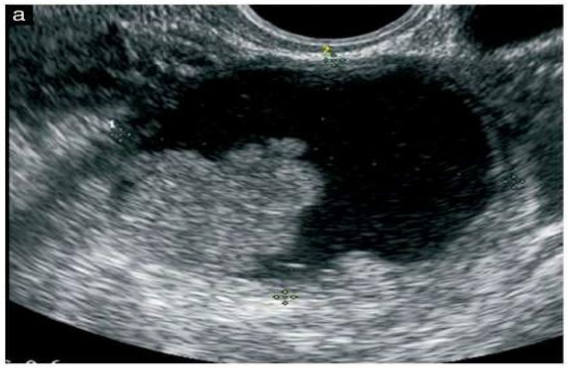
- Papillation with blood flow
  - may be a sign of malignisation in an endometriotic cyst
  - odds ratio for malignancy in any ovarian mass 3.23 (IOTA 1066 mas
- A more inhomogenous cyst content
  - tumor secretions or tumor enlargement
- Postmenopausal status





is most probably not a benign mass

Sonographic characteristics of malignant transformation in endometrioid cysts



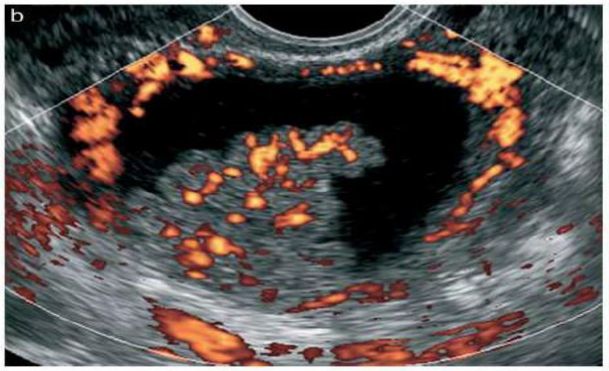
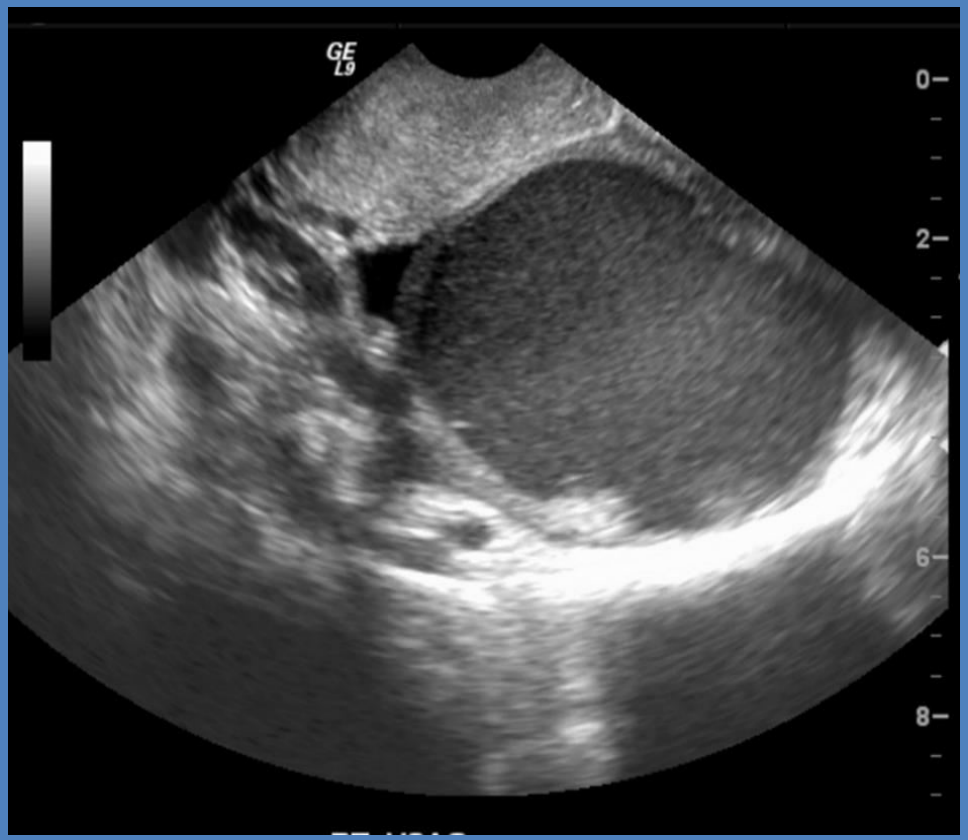
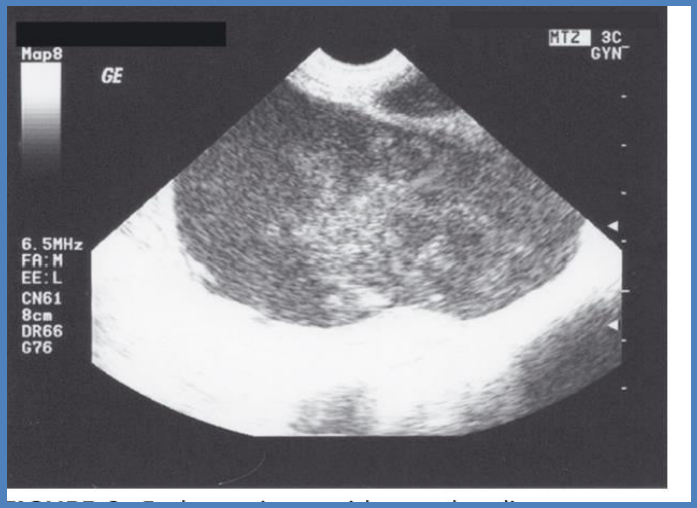
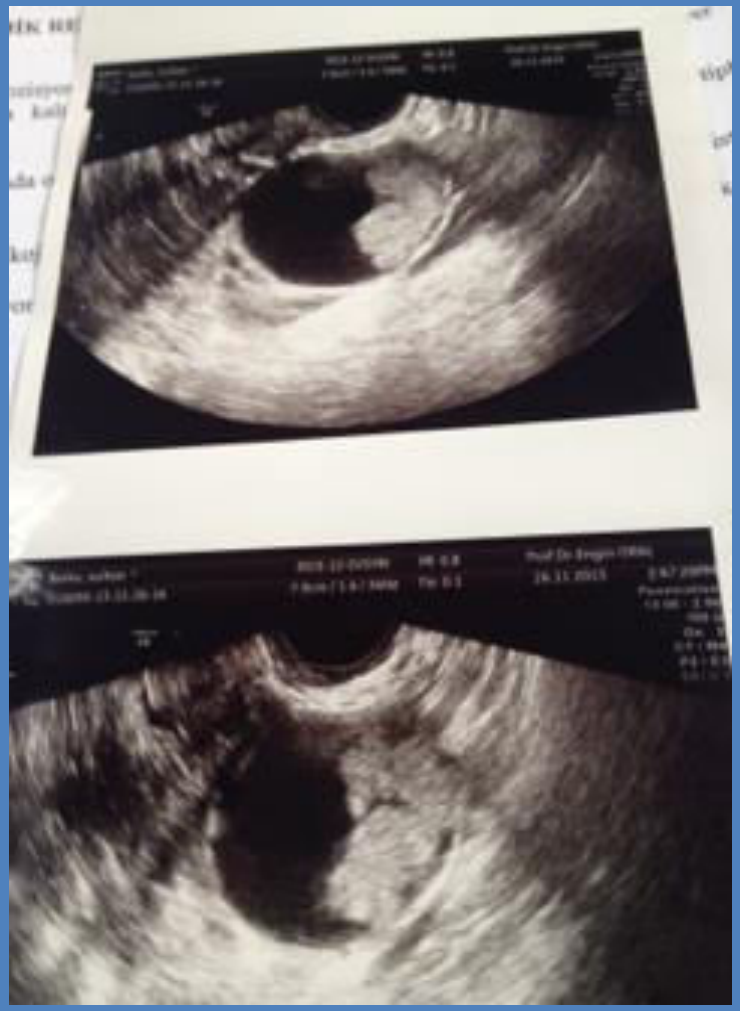


Figure 1 Endometrioid borderline tumor that developed in an endometrioid cyst in a 30-year-old patient. The ovarian lesion appeared as a unilocular-solid lesion (largest diameter of mass, 46 mm) with a papillary projection (height = 29 mm) (a), which was highly vascularized at power Doppler examination (b).

USG

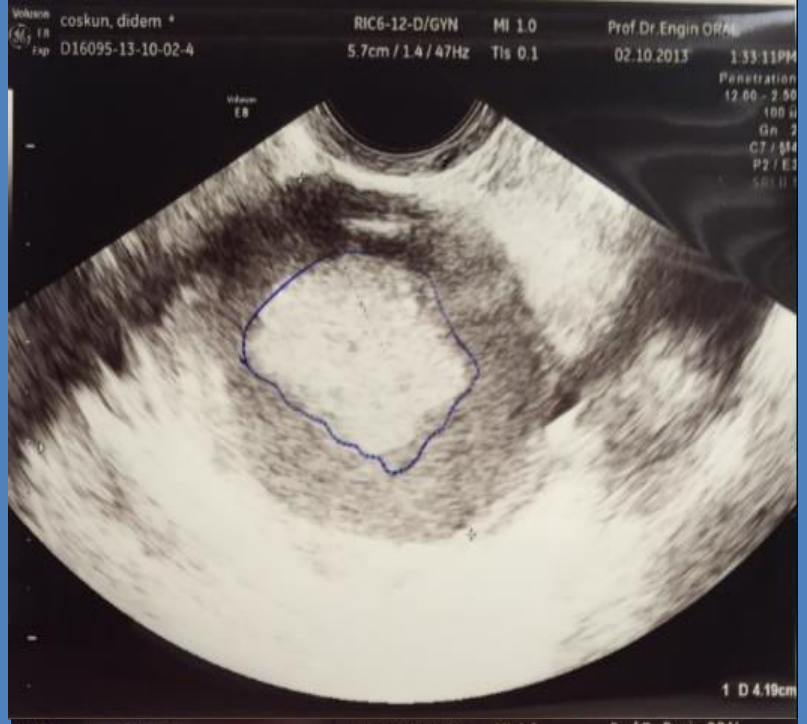


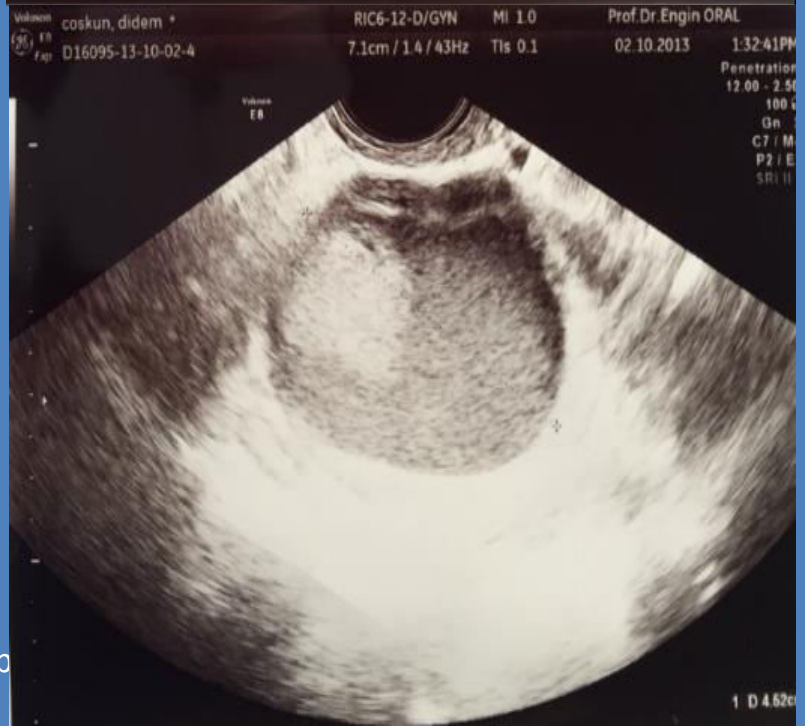




CASE 1

- A.D.C.
- Age 52, single
- **20.05.2013**
- **2006**
- LSK: left tubaovary abscess left salpengectomy
- HE4: 42.5 pmol/L Roma : 5.4
- CA125: 33
- CA19.9: 1
- Smear: Class1
- Adenomyozis
- Right ovary 2cm endometriosis
- Left ovary 4 cm endometriosis
- **23.10.2013**
- TAH +BSO
- Right Ovary: Clear Cell Carsinom
- No capsule invasion
- No surface involment
- Left Ovary: Endometriozis and Corpus Luteum
- **4.11.2013**
- Pelvic para-aortık lymphadenectomy omentectomy and ap
- Not Lymph Node Metastase





Case 2

- A.B, married
- G0P0, infertility
- Age 30
- Dysmenorrhoea
- **02.03.2015**
- **HE4**: 23.8 Roma : 1.5 **CA125**: 49
- AMH: 2.5
- **2015** bilaterally cystectomy
- Frozen:

Left ovary mucinous borderline ca

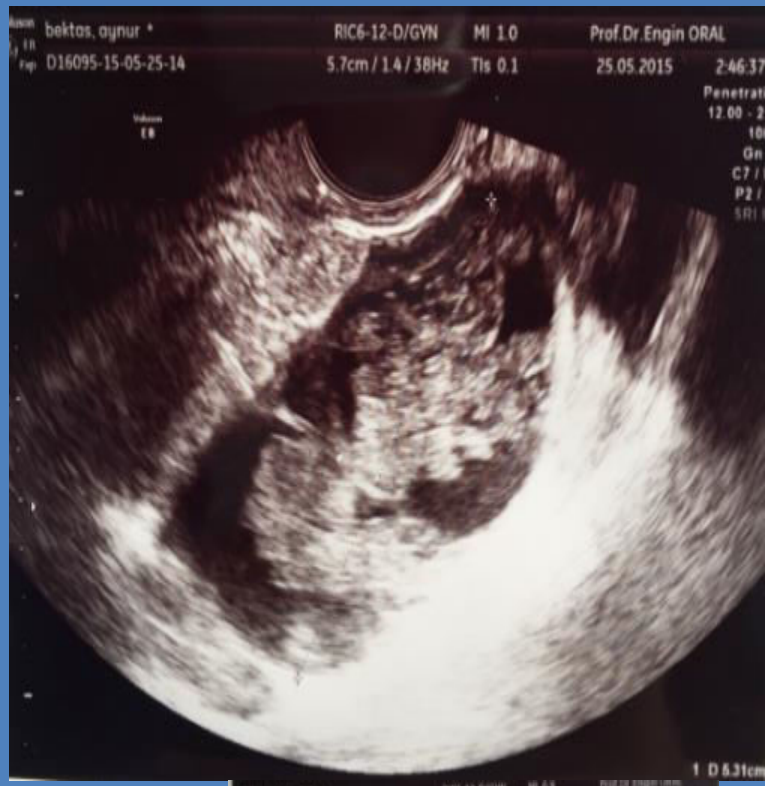
Right ovary suspect borderline ca

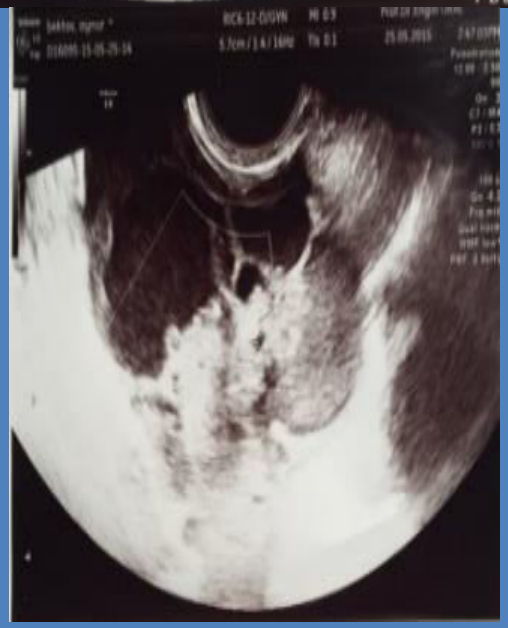
Partial omentectomy and appendectomy

Pathology:

Abdominal fluid: atypical epithelialcells in large quantities

- Right Ovary:
- Borderline seromucinous Ca(endoservical type borderline mucinous Ca)
- Left Ovary:
- Borderline seromucinous Ca (endoservical type borderline mucinous Ca)





CA-125

- **CA-125 has been shown to be a poor screening modality for endometriosis-associated ovarian cancers as well as non-endometriosis ovarian cancers**
- **Wang et al found that CA-125 levels were lower in endometriosis-associated ovarian carcinoma compared to patients with non-endometriosis ovarian carcinoma (mean 122.9 versus 1377.5 respectively)**
- **Lim et al found that 32.6% of patients with early stage endometriosis-associated ovarian carcinoma demonstrated normal CA-125 levels**

Wang S et al. Clinical analysis of ovarian epithelial carcinoma with coexisting pelvic endometriosis. Am J Obstet Gynecol 2013;208:413.e1-5.

Lim MC et al. Clinical presentation of endometrioid epithelial ovarian cancer with concurrent endometriosis: a multi-center retrospective study. Cancer Epidemiool Biomarkers Prev 2010;19:398-404.

What is the role of tumor markers, HE4 (**Human Epididymis Protein 4)** and CA 125, in differential diagnosis of endometrioma and ovarian malignancies?

- Similar sensitivity to CA 125 when comparing serum from *ovarian cancer cases to* ***healthy controls***
- Higher sensitivity when comparing ovarian cancer cases to **benign gynecologic disease**
- There are some data suggesting that human epididymal antigen (HEA) 4 is a better indicator than Ca-125 to distinguish epithelial ovarian cancers from pelvic endometriosis and pelvic inflammatory diseases especially in premenopausal women

2013

Anastasi *et al. Journal of Ovarian Research* 2013, **6**:44
http://www.ovarianresearch.com/content/6/1/44

JOR JOURNAL OF OVARIAN RESEARCH

RESEARCH Open Access

The use of HE4, CA125 and CA72-4 biomarkers for differential diagnosis between ovarian endometrioma and epithelial ovarian cancer

Emanuela Anastasi[1], Teresa Granato[2], Renato Falzarano[1], Paola Storelli[3], Adele Ticino[3], Luigi Frati[1], Pierluigi Benedetti Panici[3] and Maria Grazia Porpora[3*]

Grup 1. Adneksiyal patoloji yok
Grup 2. Bening adneksiyal yapılar
Grup 3. Endometrioma
Grup 4. Ovarian kanser

According to the indications of the manufacturer of the HE4 EIA assay, an index ≥13.1% and ≥27.7% indicates a high risk for the presence of EOC in pre- and postmenopausal women, respectively

Table 2 Serum markers for each group

	n	Group 1	Group 2	Group 3	Group 4
		50	17	57	39
CA125	Mean	16.8	19.9	46.1	1976.3
U/mL	SD	8.6	20.5	34	7390.4
	Median(range)	14 (9–47)	13 (9–97)	38 (8–167)[a]	480 (8–46210)[a,b]
HE4	Mean	48.6	60.6	53.8	508.3
pmol/L	SD	13.6	26.5	15.3	301.5
	Median(range)	47 (24–103)	58 (30–125)	53 (26–98)	426 (48–850)[a,b]
CA72-4	Mean			3	39.8
U/mL	SD			0.98	45.1
	Median(r			2.7 (1.8 -6.2)	7 (1–112)[a,b]

[a]p-value < 0.05 vs Group 1 (healthy

4 (ovarian cancer).

Table 3 Sensitivity, specificity, PPV and NPV of controls and malignant *vs* benign cases for each marker

	CA125	HE4	CA72-4
Sensitivity %	90	87	67
Specificity %	70	100	96
PPV	51	100	84
NPV	95	96	89

Cut-off levels: CA125 = 35 U/mL; HE4 = 150 pmol/L; CA72-4 =3.8 U/mL.

Utility Serum Marker HE4 for the Differential Diagnosis Between Endometriosis and Adnexal Malignancy

2016

(*Int J Gynecol Cancer* 2016;26: 52–55)

Ignacio Zapardiel, PhD, Mikel Gorostidi, MD,† Antonella Ravaggi, MD,‡ Maria T. Allende, PhD,§ Margarida Silveira, PhD,|| Daniel Abehsera, PhD,* and Ronalds Macuks, PhD¶*

- We collected 981 healthy patients diagnosed with adnexal patology and selected 65 patients diagnosed with endometriosis and analyzed their serum markers CA125, HE4, and Risk of Ovarian Malignancy Algorithm (ROMA) index. In total, 642 (65.4%) patients presented with a pelvic mass, with 324 (33%) of them being diagnosed with malignant disease.
- HE4 was positive only in 1.5% of cases, CA125 in 64.6%, and ROMA index in 14.1%.
- Conclusions: The HE4 serum marker showed similar sensitivity, but better specificity, than CA125 and can improve the detection of malignant pathology in women diagnosed with **adnexal pathology.HE4 can be a very useful biomarker to exclude malignant disease in patients with endometriosis**

How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

Identification of all women with endometriosis, either surgically documented or self-reported by symptoms

- Hormonal treatment/pregnancy aimed at reducing the risk of recurrent endometriosis and endometriomas
- Careful follow up of ovarian endometriomas with imaging studies, particularly MRI when Us is suspicious, to detect any characteristics changes such as mural formation.
- Fertility preservation ;embro,egg or tissue preservation should be considered
- **Complete excision of endometriosis be proposed to peri-or postmenopausal women**

Summary of combined oral contraceptive (COC) use and risk of cancer

Studied relation	Reference	Type	Level of evidence	Material	Main findings	Relative risk (95% confidence interval)
Use of COC in relation to risk of epithelial ovarian cancer	Beral *et al.* [2008]	Meta-analysis	2	23,257 cases 87,303 controls	• Decreased risk in COC ever users • A more pronounced effect by duration of use	0.73 (0.70–0.76)
	Havrilesky *et al.* [2013]	Systematic review/ meta-analysis		657,055 women, 3,981,072 women years	• The protective effect lasts at least 30 years after use	0.73 (0.66–0.81)
	Hannaford *et al.* [2007]	Prospective cohort	2	46,000 women 744,000 women years	• Decreased risk in COC ever-users • A more pronounced effect by duration of use	0.54 (0.40–0.71)
	Vessey and Painter [2006]	Prospective cohort		17,032 women, 540,000 women years	• The protective effect lasts at least 15–20 years	0.5 (0.3–0.7)

Original Research

Ovarian cancer (incidence rate ratio, 0.67; 99% confidence interval, 0.50-0.89)

2017

GYNECOLOGY

Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study

Lisa Iversen, PhD; Selvaraj Sivasubramaniam, MSc; Amanda J. Lee, PhD; Shona Fielding, PhD; Philip C. Hannaford, MD

Brynhildsen J. Combined hormonal contraceptives: prescribing patterns, compliance, and benefits versus risks. Ther Adv Drug Saf. 2014 Oct;5(5):201-13

How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

- Treatment planning:
  - Complete surgical resection of all endometriotic foci in women undergoing surgical treatment, with tissue evaluation of ovarian endometriomas to rule out malignancy
  - Oophorectomy and Salpingectomy Should be individualized and offered Base on the patients Risk and desires

AOGS MAIN RESEARCH ARTICLE

Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer

2013

ANNA-SOFIA MELIN[1,2], CECILIA LUNDHOLM[1], NINOA MALKI[1], MARJA-LIISA SWAHN[2], PÄR SPARÈN[1] & AGNETA BERGQVIST[1,3]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, [2]Department of Obstetrics and Gynecology, Karolinska University Hospital, Huddinge, and [3]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Stockholm, Sweden

- All women with a 1st time discharge Dx of endometriosis between 1969 – 2007 in Sweden [National Swedish Patient Register]

- Identified all women Dx with epithelial ovarian cancer [National Swedish Cancer Register] at least 1 year after the endometriosis Dx

Acta Obstet Gynecol Scand. 2013

AOGS MAIN RESEARCH ARTICLE

Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer

ANNA-SOFIA MELIN[1,2], CECILIA LUNDHOLM[1], NINOA MALKI[1], MARJA-LIISA SWAHN[2], PÄR SPARÈN[1] & AGNETA BERGQVIST[1,3]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, [2]Department of Obstetrics and Gynecology, Karolinska University Hospital, Huddinge, and [3]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Stockholm, Sweden

- Strong reduction in risk of epithelial ovarian CA:
  - One-sided oophorectomy involved with Endometriosis , multivariate analysis (OR 0.19, 95%CI 0.28-0.62) 81% reduction.
  - Complete extirpation of endometriotic tissue (OR 0.30, 95%CI 0.25-0.55) 70% reduction

Acta Obstet Gynecol Scand. 2013

Adenomyosis-Endometrial Cancer

- The reported incidence of the presence of these 2 conditions in hysterectomy specimens is variable, ranging from 10–70%.The mechanism of the development of endometrial cancer in patients with adenomyosis remains unclear. Previous reports have suggested that adenomyosis can undergo malignant transformation and may be a precursor lesion to adenocarcinoma (Mittal and Barwick, 1993; Kucera et al., 2011). However, no study has demonstrated the natural transformation of adenomyosis to adenocarcinoma
- It has been reported that endometrial cancers involving adenomyosis was associated with a low histologic grade, a history of hormonal use and more favorable prognosis (Ismiil et al., 2007a). However, other data suggest that adenomyosis is related with deep myometrial invasion (Ismiil et al., 2007b).
- Musa et al. (2012) found that there was a close relationship between adenomyosis and lower tumor grade, less myometrial invasion, negative lymphovascular space invasion and negative lymph nodes (Musa et al., 2012). This result shows that endometrioid tumor with adenomyosis are hormonally responsive, well differentiated, and more likely to be diagnosed earlier while it would be still confined to uterus

Arch Gynecol Obstet
DOI 10.1007/s00404-017-4375-z

GYNECOLOGIC ONCOLOGY

Endometrial cancer arising in adenomyosis versus endometrial cancer coexisting with adenomyosis: are these two different entities?

Hiroko Machida[1] · Midori Maeda[4] · Sigita S. Cahoon[1] · Christopher A. Scannell[3] · Jocelyn Garcia-Sayre[1] · Lynda D. Roman[1,2] · Koji Matsuo[1,2]

2017

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- EC-AIA cases were identified via a systematic literature search (n = 46).
- EC-A cases were identified from a historical cohort that underwent hysterectomy-based surgical staging in two institutions (n = 350).
- The EC-AIA group was significantly older than the EC-A group
- The EC-AIA group was significantly associated with more non-endometrioid histology and deep myometrial tumor invasion
- Tumor grade, stage, and nodal metastasis risk were similar.
- In a univariate analysis, the EC-AIA group had a significantly decreased DFS compared to EC-A (5-year rates, 72.2 versus 85.5%, p = 0.001).

Conclusion Our study demonstrated that EC-AIA has distinct tumor characteristics and a poorer survival outcome compared to EC-A.

THE JOURNAL OF
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Clear cell adenocarcinoma arising from adenomyotic cyst: A case report and literature review

2016

Akira Baba[1], Shinji Yamazoe[1], Murat Dogru[1], Mariko Ogawa[2], Kiyoshi Takamatsu[2] and Jun Miyauchi[3]

[1]Department of Radiology, [2]Obstetrics and Gynecology, and [3]Pathology and Laboratory Medicine, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan

Table 1 Demographic and clinical characteristics of cases with clear cell adenocarcinoma and adenomyotic uterine cysts in the literature

Reported Cases	Age	Complaint	Endometrial Cytology	Presurgical Diagnosis	Radiological Findings	Stage	Histopathology	Surgery	Chemotherapy/ Radiotherapy	Prognosis
Case 1 (Mori *et al.* 1994)	63	Uterine bleeding	Negative	Degenerative myoma	CT: Muscle layer isodense cystic mass	II	Atrophic endometrium adenomyosis CCAC, hobnail (+)	TrA Hys + BSO+ pelvic LNS	CAP 3 course	Alive at 14 months
Case 2 (Koshiyama *et al.* 2002)	72	Pain	Negative	Ovarian cancer	MRI: Cystic pelvic mass	Ic	Atrophic endometrium adenomyosis CCAC	TrA Hys + BSO	Rx (5000 rad)	ILNM, expired at 60 months
Case 3 (Ohta *et al.* 2008)	54	Hypermenorrhea	Negative	Myoma	CT/MRI: Uterine myoma + ovary CA	IV	Adenomyosis CCAC, hobnail (+)	TrA Hys + BSO + O	Cx (DU)	LM, OM, expired at 7 months
Case 4 (Hirabayashi *et al.* 2009)	73	Fever, weight loss	Negative	Myoma	CT/MRI: Uterine solid mass + PALNM+ LSCLNM	IV	Adenomyosis CCAC, hobnail (+)	TrA Hys + BSO	Paclitaxel carboplatin, 3 cycles	Alive at 7 months
Case 5 (Jeoung Shin *et al.* 2011)	52	Uterine bleeding, pain	Negative	Myoma	CT/MRI: Uterine cystic mass	III	Adenomyosis CCAC	VHys + BSO+ PL + PAL + O	Paclitaxel carboplatin, 3 cycles + Rx (5040 cGy)	DU
Case 6 (Baba *et al.* 2014)	40	Polyuria mass sensation	Negative	Myoma	CT/MRI: Uterine cystic mass	Ib	Adenomyosis CCAC, hobnail (+)	TrAHys	Patient refused	Alive at 6 months

CA, carcinoma; CCAC, clear cell adenocarcinoma; CT, computed tomography; Cx, chemotherapy; DU, details unknown; ILNM, inguinal lymph node metastasis; Hys + BSO, transabdominal hysterectomy + bilateral salphingoopherectomy; LM, liver metastasis; LSCLNM, left subclavian lymph node metastasis; MRI, magnetic resonance imaging; OM, omentum metastasis; PALNM, para-aortic lymph node metastasis; Rx, radiotherapy; TrA Hys + BSO + O, transabdominal hysterectomy + bilateral salphingoopherectomy + omentectomy; TrA Hys + BSO + Pelvic LNS, transabdominal hysterectomy + bilateral salphingoopherectomy + pelvic lymph node sampling; VHys + BSO + PL + PAL + O, vaginal hysterectomy + bilateral salphingoopherectomy + pelvic lymphadenectomy + paraaortic lymphadenectomy + omentectomy.

Endometriosis associated Extra Ovarian Malignancy

- Extragonadal sites are affected in one-fourth to one-fifth of all cases
- Since the malignant transformation can take place in every site affected by endometriosis, extragonadal malignancies can be found in the lower pelvis, gastrointestinal tract, abdominalwall, umbilicus, pleura and others .
- The most common localisations of extragonadal malignancies are the rectosigmoid, colon, rectovaginal septum and pelvic peritoneum; these sites are commonly involved by deep infiltrating endometriosis
- ***Endometrioid carcinoma (66 %)***
- ***Adenosarcoma (25 %)***

EXTRAOVARIAN ENDOMETRIOSIS ABDOMINAL WALL

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CASE REPORT

Endometrial stromal sarcoma in the abdominal wall arising from scar endometriosis

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Departments of [1]Obstetrics and Gynecology, Bagcilar Training and Research Hospital, [2]Plastic and Reconstructive Surgery, Bezmialem Foundation University and [3]Obstetrics and Gynecology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey

Gynecologic Oncology Reports 8 (2014) 10–13

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Case Report

Malignant transformation of abdominal wall endometriosis with lymph node metastasis
Case report and review of literature

Francesc Fargas Fàbregas *, Maite Cusidó Guimferrer, Francesc Tresserra Casas, Sonia Baulies Caballero, Rafael Fábregas Xauradó

Instituto Universitari Dexeus, Barcelona, Spain

- The probability of developing endometriosis in a surgical scar is roughly 0.03–1%,
- **Malignant transformation is likely to occur in 0.3 to 1% of the cases,**

CASE REPORT

Malignant transformation of abdominal wall endometriosis to clear cell carcinoma: case report and review of the literature

Anne Sophie Bats, M.D.,[a] Yaelle Zafrani, M.D.,[a] Patricia Pautier, M.D.,[b] Pierre Duvillard, M.D.,[c] and Philippe Morice, M.D.[a]

Departments of [a] Surgery, [b] Oncology, and [c] Pathology, Institut Gustave Roussy, Villejuif, France

Objective: To report a case of clear cell carcinoma in abdominal wall endometriosis after cesarean section.
Design: Case report.
Setting: A French oncology center.
Patient(s): A 38-year-old woman who developed a 10-cm mass in the abdominal wall muscles, 13 years after a cesarean section.
Intervention(s): Abdominal wall resection and chemotherapy.
Main Outcome Measure(s): Clinical outcome.
Result(s): The diagnosis of clear cell carcinoma in abdominal wall endometriosis was confirmed, and wide surgical excision with abdominal wall reconstruction was performed after three courses of chemotherapy.
Conclusion(s): The malignant transformation of abdominal wall endometrioma has not been clearly elucidated, owing to its rarity. However, the eventuality should always be considered, and the prognosis improved through wide surgical excision. (Fertil Steril® 2008;90:1197.e13–e16. ©2008 by American Society for Reproductive Medicine.)

Key Words: Abdominal wall endometrioma, malignant transformation, clear cell carcinoma

Endometriosis-Associated Abdominal Wall Cancer

A Poor Prognosis?

2015

(*Int J Gynecol Cancer* 2015;25: 1633–1638)

Lara Taburiaux, MD, Nicola Pluchino, MD, Patrick Petignat, MD, and Jean-Marie Wenger, MD

- Endometriosis-associated abdominal wall cancer (EAAWC) is rare, and few reports are available.
- The mean age of the patients at the time of diagnosis was 47 years (range of 38-60 years)
- In all of these patients, EAAWCwas described after uterine surgery (mostly cesarean section).
- The delay between the first surgery and the diagnosis of malignant disease was more than 20 years.
- Clear cell carcinoma was the most common histology, followed by endometrioid carcinoma.
- Death was described in 44% of women within a few months of diagnosis.

Ferrandina et al. World Journal of Surgical Oncology (2016) 14:300
DOI 10.1186/s12957-016-1054-7

World Journal of Surgical Oncology

2016

CASE REPORT Open Access

CrossMark

Endometriosis-associated clear cell carcinoma arising in caesarean section scar: a case report and review of the literature

N:22

Gabriella Ferrandina[1,2*], Eleonora Palluzzi[2], Francesco Fanfani[3], Stefano Gentileschi[4], Anna Lia Valentini[5], Maria Vittoria Mattoli[6], Ilaria Pennacchia[7], Giovanni Scambia[2] and Gianfranco Zannoni[7]

Table 1 Clear cell carcinoma arising from endometriosis of the scar caesarean section

	Age	Previous uterine surgeries	Months since symptoms	Size cm	FNA or biopsy	Primary treatment	Pathology	Adjuvant treatment	Relapse	Death
Schnieber Agner-Kolb 1986 [4]	40	1 CS 15 years before	–	–	–	WE, BSO, Hys	Mass: CCC + endometriosis Ovaries and uterus: negative	RT, progestins	–	Yes after 18 months
Hitti 1996 [5]	46	1 CS 14 years before 1 CS 12 years before	–	6	–	WE, BSO, Hys	CCC + endometriosis	RT	No after 30 months	No after 30 months
Miller 1998 [6]	38	1 hysterotomy 9 years before 1 abortion 3 years before 1 CS 2 years before	8	4	CCC + endometriosis	WE, BSO, Hys omentectomy	Scar: CCC Ovaries, uterus, omentum: negative Margins: close	CIS-based CT RT	No after 60 months[a]	No after 60 months[a]
Park 1999 [7]	56	1 CS 24 years 1 CS 20 years	–	5	–	WE	Mass: CCC + endometriosis	RT	–	–
Ishida 2003 [8]	56	1 CS 24 years 1 CS 20 years	7	10	Endometrial carcinoma	WE, Hys, BSO	Mass: CCC Ovaries and uterus: negative	CIS-based CT	–	Yes after 24 months[b]
Sergent 2006 [9]	45	1 CS 25 years 1 CS 23 years 2 excisions of benign endometriosis nodules at the scar	17	20	–	WE, BSO, later on: endometrial curettage	Mass: CCC + endometriosis Right ovary: benign endometriosis; left ovary and uterus: negative Margins: 1 cm free	Not done	Yes early after surgery[a]	Yes after 6 months
Alberto 2006 [10]	38	1 CS 11 years BSO, Hys for endometriosis	6	6	–	WE	CCC	Carbo/PTX RT	–	–
Razzouk 2007 [11]	46	1 CS 26 years before 1 CS 24 years before 2 excisions of endometriosis nodules at the scar	–	>20	–	GnRh analogue without benefit WE, BSO	Mass: CCC + endometriosis Ovaries: negative LN: 1 positive	Carbo/PTX	Yes during CT	Yes after 6 months[b]
Rust 2008 [12]	42	3 CS Hys 5 years before	24	5	Carcinoma	WE	Mass: CCC + endometriosis Margins: 1 mm free	Not done	–	–
Bats 2008 [13]	38	1 CS 13 years before 1 excision of endometriosic nodule at the scar	–	10	Atypical cells	NACT (carbo/PTX) No benefit WE, BSO, Hys, omentectomy	Mass: CCC + endometriosis Uterus: adenomyosis Other specimens: negative Margins: 2 mm free	Not done	Yes after 4 months[a]	–
Williams 2009 [14]	53	1 CS 17 years before	24	2.5	CCC (excisional biopsy)	WE of the scar, BSO, Hys, omentectomy Inguinal/Pelvic LNctomy	Mass: CCC Uterus, right ovary, omentum: negative, left ovary: teratoma Inguinal LN: 7 positive/11 Pelvic LN: 8 positive/14	Carbo/PTX (4 cycles)	Yes after 3 months[a]	Yes after 11 months[b]
Boudel 2010 [15]	43	1 CS 20 years before 1 CS 15 years before 1 excision of endometriosic nodule at the scar	9	9	–	WE, partial resection of pubic symphysis, umbilicus, right rectus abdomen, pelvic LN sampling Later on: BSO, Hys	Mass: CCC + endometriosis Pelvic LN: multiple positive Ovaries, uterus: negative	Carbo/PTX (6 cycles) RT	Yes after 6 months[a]	Yes after 22 months[b]

Table 1 Clear cell carcinoma arising from endometriosis of the scar caesarean section *(Continued)*

Yan 2011 [16]	41	2 CS 5 years before 2 excisions of benign endometriosic nodule at the scar 1 year and 4 months before	4	9	Not done	Progestins without benefit WE	Mass: CCC	CT	No after 24 months[d]	No after 24 months[d]
Li 2012 [17]	49	1 CS 26 years before	25 years	9	Not done	WE, Hys, BSO	Mass: CCC Uterus, ovaries: negative	Carbo/PTX (6 cycles)	No[c] after 8 months	No[c] after 8 months
Mert 2012 [19]	42	Tubal ligation, right ovariectomy	–	15	Tumor cells Mullerian origin	NACT (carbo/PTX) WE, left SO Hys, left Pelvic LNctomy Omentectomy	Mass: CCC + endometriosis Other organs: negative Margins: free	Not done	No after 1 month[a]	No After 1 month[a]
	51	2 CS Hys for myomas	12	6	Excisional biopsy CCC + endometriosis	BSO, Omental biopsy	Negative Margins: free	RT	No after 31 months[b]	No after 31 months[b]
Shalin 2012 [18]	47	1 CS	10	3	CCC	WE, left ovary cystectomy, endometrial biopsy, pelvic LN sampling	Mass: CCC + endometriosis Ovarian cyst: endometriosis Endometrium: negative Pelvic LN: 2 positive/4 Margins: positive	CIS-based CT (6 cycles) RT	Yes after 5 months[b]	No after 7 months[b]
Ijichi 2014 [20]	60	1 CS 37 years before 1 CS 35 years before	48	4	Atypical cells	WE	Mass: CCC + endometriosis Margins: free	Not done	Yes after 8 months[a]	No after 23 months[a]
Aust 2015 [21]	47	1 CS 16 years before vaginal Hys 10 years before	6	10	–	WE Later on: BSO, pelvic, aortic LNctomy omentectomy	Mass: CCC Ovaries and omentum: negative LN:2 positive/48 Margins: free	Carbo/PTX (6 cycles)	No after 10 months[c]	No after 10 months[c]
Heller 2014 [22]	37	1 CS 1 CS 1 CS 8 years before	96*	18	CCC	WE, left SO, pelvic LNctomy	Mass: CCC Ovary: negative LFN: multiple LN positive	Refused treatment	Yes after 5 months[a]	–
Liu 2014 [23]	39	1 CS 1 excision of endometriosic nodule at the scar	60	6	–	WE, partial cystectomy, BSO, Hys, omentectomy, inguinal,pelvic, aortic LNctomy	Mass: CCC + endometriosis Ovaries, uterus, omentum: negative Bladder: positive Pelvic LN: 18 positive/21 Aortic LN: 6 positive /6 Inguinal LN: 8 positive/8	Carbo/PTX (3 cycles)	YES after 10 months[c]	Yes after 12 months[c]
Sosa-Dután 2015 [24]	45	1 CS 1 CS 1 CS	6	9	–	WE, margins: 2 cm free	Mass: CCC + endometriosis	Not done	No after 16 months[a]	No after 16 months[a]
Current case	44	1 CS 9 years before	8	22	Endometrial carcinoma	NACT (carbo/PTX) WE, BSO, Hys, inguinal, and pelvic LNctomy	Mass: CCC + endometriosis Ovaries, uterus: negative Pelvic LN: 7 positive/14 Inguinal LN: 8 positive/11 Margins: free	Not done	Yes after 2 months from surgery	Yes after 6 months

CCC clear cell carcinoma, *CS* caesarean section, *WE* wide mass excision, *BSO* bilateral salpingo-oophorectomy, *SO* salpingo-oophorectomy, *Hys* hysterectomy, *LNctomy* lymphadenectomy, *LN* lymph node, *Carbo* carboplatin, *CIS* cisplatin, *PTX* paclitaxel, *RT* radiotherapy

*The mass was reported to have come and gone over the last 8 years since the last CS

[a]From surgical resection

[b]From initial diagnosis

[c]Since completion of chemotherapy

[d]Not specified

Curr Oncol Rep (2016) 18:68
DOI 10.1007/s11912-016-0552-7

SARCOMAS (SR PATEL, SECTION EDITOR)

Uterine Adenosarcoma: a Review

Michael J. Nathenson[1] · Vinod Ravi[2] · Nicole Fleming[3] · Wei-Lien Wang[4] · Anthony Conley[2]

2016

- Adenosarcomas are rare malignancies of the femalegenital tract, accounting for approximately 5 % of uterine sarcomas.
- Occasionally, adenosarcoma occurs in the ovaries or in extra-uterine tissue, which may be related to endometriosis.
- Many of these extra-uterine adenosarcoma cases, at least, those within the abdomen or pelvis, reportedly arise in the setting of endometriosis or in patients with a history of endometriosis
- While endometriosis may be a risk factor for the development of adenosarcoma, it is likely not the sole risk factor.

Gynecologic and Obstetric Investigation
Gynecol Obstet Invest
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Published online: September 13, 2016

Malignant Transformation of Vaginal Endometriosis – A Review of Literature

2016

Mauro Cozzolino[a] Dimitrios Nasioudis[b] Giovanni Sisti[a]
Maria Elisabetta Coccia[a]

- A total of 23 eligible studies were identified and included in the present review providing information for 37 patients.
- Endometrioid adenocarcinoma (17 cases) was the most common histological subtype followed by endometrial stromal sarcoma (6 cases).
- Vaginal cancer arising from endometriosis is exceedingly rare.

Other Gynecological Cancers

Endometrial cancer

Study design	year	studies	OR, SIR or RR or HR	95% CI
Cohort	1997	Brinton et al.	1.09	0.6– 1.9
Cohort	2002	Olson et al.	1.20	0.57– 2.53
Cohort	2005	Brinton et al.	0.82	0.3– 1.9
Cohort	2006	Melin et al.	1.19	0.96–1.46
Cohort	2007	Melin et al.	1.14	0.93–1.39
Case– control	2004	Borgfeldt and Andolf	0.58	0.42– 0.81
Case–control	2005	Brinton et al.	1.23	0.63–2.38
Case-control	2015	Yu HC et al.	2.83	1.49-5.35

- ✓ Data on the association between endometriosis and endometrial cancer was inconsistent
- ✓ Low number of cases

Cancer Causes Control (2017) 28:437–445
DOI 10.1007/s10552-017-0856-4

CrossMark

ORIGINAL PAPER

Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses

Elizabeth M. Poole[1] · Wayne T. Lin[2] · Marina Kvaskoff[1,3] · Immaculata De Vivo[1,4] · Kathryn L. Terry[2,4] · Stacey A. Missmer[1,2,4,5]

2017

Table 1 Age-standardized characteristics of NHSII participants at midpoint of follow-up (1999)

	No endometriosis ($n=86,930$)	All self-reported endometriosis ($n=8,226$)	Laparoscopically confirmed endometriosis ($n=5,910$)	Self-reported endometriosis without laparoscopic confirmation ($n=2,316$)

- Over 18 years of follow-up, we identified 228 ovarian and 166 endometrial cancers among 102,025 and 97,109 eligible women, respectively.
- Self-reported endometriosis was associated with ovarian cancer [relative risk (RR): 1.81; 95% confidence interval (CI): 1.26–2.58]; this association was stronger for laparoscopically confirmed endometriosis (HR: 2.14; 95% CI 1.45–3.15).
- **No association was observed with endometrial cancer (self-report RR: 0.78; 95% CI 0.42–1.44; laparoscopic-confirmation RR: 0.76; 95% CI 0.35–1.64).**

Breast Cancer Res Treat (2016) 159:545–552
DOI 10.1007/s10549-016-3957-y

EPIDEMIOLOGY

A prospective study of endometriosis and risk of benign breast disease

2016

Leslie V. Farland[1,2] · Rulla M. Tamimi[1,3] · A. Heather Eliassen[1,3] · Donna Spiegelman[1,3,4] · Laura C. Collins[5] · Stuart J. Schnitt[5] · Stacey A. Missmer[1,2,3]

- Among women in the Nurses' Health Study II followed from 1991–2003 (n = 76,393),
- we investigated the association between laparoscopically confirmed endometriosis and biopsy-confirmed BBD.
- Endometriosis was associated with a modest increased risk of biopsy-confirmed BBD in crude and multivariable adjusted models (HR 1.20, 95 % CI 1.00–1.43).

Original Research

Laparoscopically Confirmed Endometriosis and Breast Cancer in the Nurses' Health Study II

2016

Leslie V. Farland, ScD, Rulla M. Tamimi, ScD, A. Heather Eliassen, ScD, Donna Spiegelman, ScD, Susan E. Hankinson, ScD, Wendy Y. Chen, MD, MPH, and Stacey A. Missmer, ScD

Table 2. Laparoscopically Confirmed Endometriosis in Relation to Breast Cancer Risk in the Nurses' Health Study II

Endometriosis	Cases Per Person-Year	Age and Calendar Time–Adjusted Model [HR (95% CI)]*	Multivariable-Adjusted Model [HR (95% CI)]*
Breast cancer overall			
No	4,479/2,329,489	1.0 (referent)	1.0 (referent)
Yes	500/215,434	1.07 (0.97–1.17)	0.96 (0.88–1.06)
Breast cancer by menopausal status			
Premenopausal women			
No	2,258/1,356,591	1.0 (referent)	1.0 (referent)
Yes	167/82,517	1.16 (0.99–1.35)	1.05 (0.89–1.23)
Postmenopausal women			
No	1,419/501,465	1.0 (referent)	1.0 (referent)
Yes	235/97,068	0.98 (0.85–1.13)	0.93 (0.80–1.07)
Breast cancer stratified by mode of menopause transition among postmenopausal women			
Natural menopause			
No	1,035/352,180	1.0 (referent)	1.0 (referent)
Yes	66/20,196	1.17 (0.91–1.50)	1.06 (0.82–1.36)
Any surgery (hysterectomy, oophorectomy)			
No	384/153,531	1.0 (referent)	1.0 (referent)
Yes	169/76,873	0.98 (0.82–1.18)	0.90 (0.75–1.09)

Endometriosis was not found to be associated with overall risk of breast cancer in this study;

ONCOLOGY LETTERS 11: 23-30, 2016

2016

Endometriosis and breast cancer: A survey of the epidemiological studies

A. PONTIKAKI[1], S. SIFAKIS[1] and D.A. SPANDIDOS[2]

We found 4 retrospective cohort studies, 4 case-control studies and 3 case-cohort studies that demonstrated a notable risk for developing breast cancer among women with endometriosis. By contrast, we also found 5 case-control studies, 1 prospective cohort study, 1 case-cohort study and 1 cross-sectional study that demonstrated a negative association between endometriosis and breast cancer. In conclusion, as regards the clarification of a 'robust' or 'weak' association between endometriosis and breast cancer, no definite conclusions could be drawn, due to the limited number of studies and the limitations of each of these studies

Authors/(Ref) year										iation
Moseson *et a* 1993										0.6-5.1) P=0.33 0.9-20.4) P=0.07[a]
Schairer *et a* 1997										I, 1.2-8.0)[b] I, 0.7-4.1)[c]
Brinton *et al* 1997										1.1-1.4) I, 1.2-2.6)[d]
Weiss *et al* (1999										, 0.7-1.8)[e] , 0.9-3.0)[f] , 0.7-2.5)[g]
Venn *et al* (2 1999										I, 0.71-1.54)[h]
Borgfeldt an Andolf (24) 2004										, 1.0-1.2)
Melin *et al* (2006										I 1.13-1.45)[i] I, 0.82-1.78)[j]
Melin *et al* (2 2007	(1969-2002)									I, 1.02-1.13)
Bertelsen *et al* (27) 2007	Case-cohort (1978-1998)	114,327	2,031,811	17.8	1978	236	N/A	40.6	Yes	OR, 1.10 (95% CI, 0.90-1.34)[k] OR, 2.40 (95% CI, 1.43-4.01)[l]
Nichols *et al* (28) 2011	Case-control (1992-1995)	N/A	N/A	N/A	26[m]	4,935	5,111	66.2	No	OR, 1.83(95% CI, 0.95-3.51)[m]
Kok *et al* (29) 2015	Cohort (2003-2005)	N/A	9,842	3	2266	18	9,064	31-50	No	HR, 1.15 (95% CI, 0.61-2.15)

Association between Endometriosis and Breast Cancer

- It is difficult to ascertain whether a strong correlation with endometriosis and breast cancer exists.
- Several reports support an association between these entities.
- However, the effect sizes in these studies are modest and there are an equal number of studies demonstrating no correlation.
- In fact, there exist several studies demonstrating an inverse correlation between endometriosis and breast cancer.
- It is notable that these latter studies showing no association or an inverse association largely employed more stringent statistic control for confounding variables.

The fact that many studies find an association between the two conditions and that the association is lost after controlling for confounders supports the notion that the correlation may not be causative.

Semin Reprod Med 2017;35:110–116

Human Reproduction, Vol.28, No.6 pp. 1552–1568, 2013
Advanced Access publication on March 25, 2013 doi:10.1093/humrep/det050

2013

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Consensus on current management of endometriosis

Neil P. Johnson[1,2,3,*] and Lone Hummelshoj[1], for the World Endometriosis Society Montpellier Consortium[†]

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Submitted on December 16, 2012; resubmitted on January 25, 2013; accepted on February 8, 2013

Endometriosis and cancer

(13) The relative risk and absolute risk of ovarian cancer amongst women with endometriosis is so low as not to justify routine ovarian cancer screening (strong). γ

The above represent the consensus statements from the WES Montpellier Consensus.

GPP, good practice point; α, unanimous or near-unanimous (more than 80% agreed without caveat and fewer than 5% disagreed); β, unanimous with caveat (fewer than 5% disagreed but fewer than 80% agreed without caveat); γ, majority (50–80% agreed); δ, no consensus (fewer than 50% agreed with or without caveat).

ENDOMETRIOSIS AND CANCER

ESHRE, 2014

Recommendations

The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that 1) there is no evidence that endometriosis causes cancer, 2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	GPP
The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.	GPP
The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there are no clinical data on how to lower the slightly increased risk of ovarian cancer or non-Hodgkin's lymphoma in women with endometriosis.	GPP

DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS 2014

TURKISH ENDOMETRIOSIS & ADENOMYOSIS SOCIETY GUIDELINES

www.endometriozisdernegi.com
www.endometriozis.org

- Does endometriosis increase the cancer risk?
  - Yes EAOC
- What is the impact of the age of the patient with endometriosis on the cancer risk?
  - 40 years
- Is the size of endometrioma associated with the cancer risk?
  - 9 cm
- Should histopathological investigation of the suspected endometriotic lesions or endometrioma be recommended
  - Yes
- Are there any morphologic criteria that suggest malignancy?
  - Mural nodules
- What is the role of tumor markers, HE4 and CA 125, in differential diagnosis of endometrioma and ovarian malignancies?
  - HE4 is better
- Should the women with endometriosis scanned for ovarian cancer?
  - It is not recommended

Take home message

- Screening for genetic mutations in ovarian cancer is just the beginning, and an emerging concept of a dual model of ovarian carcinogenesis
- Currently , there is not sufficient data to recommend mutation screening tests in patients with endometriosis
- USG---useful in the identification of ovarian endometrioma with homogeneous hypoechogenic cystic features and those with mural malignant changes
  - hyperdense mural nodules within the ovary and rapid growth of an endometrioma can be visualized

Take home message

- Existing epidemiological evidence linking endometriosis with ovarian cancer is insufficient to change current clinical practice.
- It is not recommended to scan the women with endometriosis for ovarian cancer due to its low incidence and the absence of effective scanning test.

Endometrioma
in a peri-or postmenopausal women is a reason for concern
link with ovarian cancer

The risk of ovarian cancer associated with different t forms of endometriosis remains to be determined!!!

Take home message

- There is no recommended cancer screening for women with endometriosis.
- There is theoretical rationale to believe that surgical and hormonal control of endometriosis may also decrease the risk of ovarian cancer.
- However, there are no data to date to support such a conclusion