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human reproduction

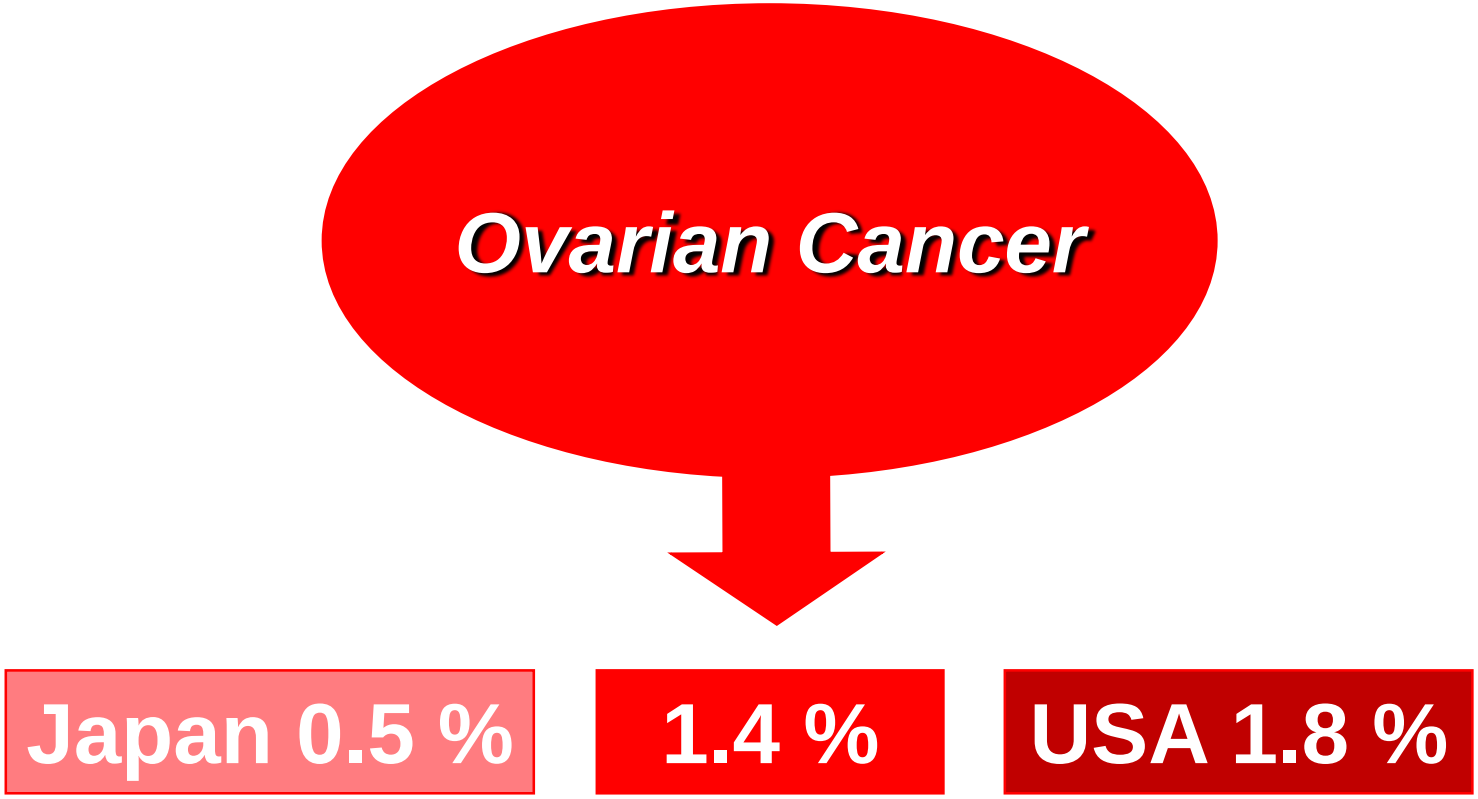
ORIGINAL ARTICLE *ESHRE pages*

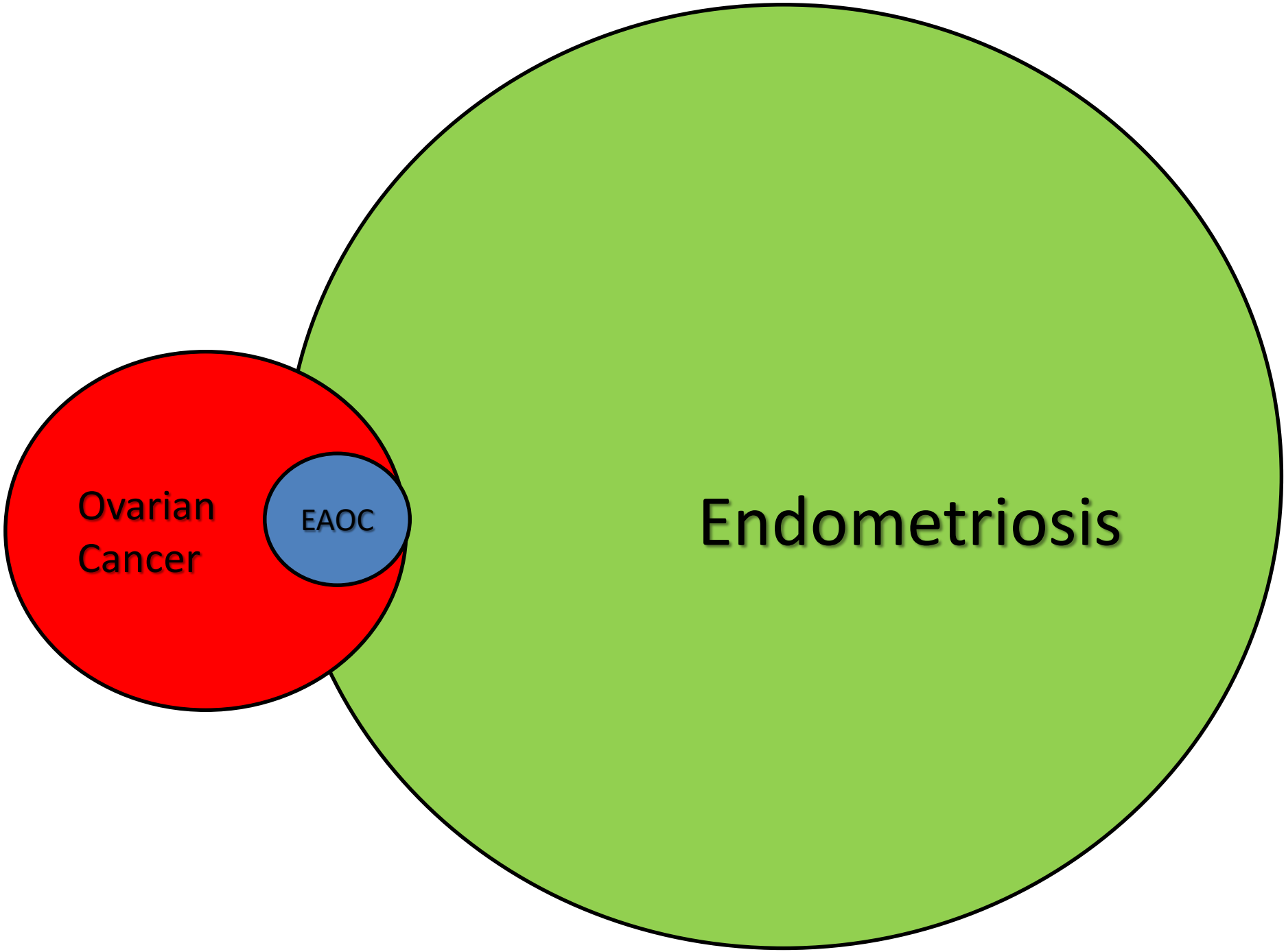
ESHRE guideline: management of women with endometriosis†

G.A.J. Dunselman[1,*], N. Vermeulen[2], C. Becker[3], C. Calhaz-Jorge[4], T. D'Hooghe[5], B. De Bie[6], O. Heikinheimo[7], A.W. Horne[8], L. Kiesel[9], A. Nap[10], A. Prentice[11], E. Saridogan[12], D. Soriano[13], and W. Nelen[14]

"… The exact prevalence of endometriosis is unknown but estimates approximately 10% of women of reproductive age, to 50% of infertile women."

Lifetime Risk in General Population




Ovarian Cancer
EAOC
Endometriosis

ARCHIVES OF SURGERY

VOL. 10 JANUARY, 1925—IN TWO PARTS—PART I No. 1

ENDOMETRIAL CARCINOMA OF THE OVARY, ARISING IN ENDOMETRIAL TISSUE IN THAT ORGAN *

JOHN A. SAMPSON, M.D.

ALBANY, N. Y.

Many interesting and important problems have presented themselves to clinicians and pathologists, who have appreciated the frequency of ectopic endometrium-like tissue in the pelvis and have had an opportunity to observe the various lesions in the ovaries and other pelvic structures resulting from this tissue. One of the most interesting problems is the source of these implantation-like lesions occurring on the surface of the various pelvic structures. Are they true implantations derived primarily from uterine or tubal epithelium escaping through the tubes into the peritoneal cavity, as the study of many of these lesions in human beings indicates [1] and as Jacobson,[2] in the autotransplantation of endometrial tissue in rabbits, has experimentally proved possible, or are they derived from scattered localized metaplasias of the serosal mesothelium or from developmental inclusions of portions of the Wolffian body or Müllerian duct? This problem has not yet been definitely solved to the satisfaction of all who are interested in the subject. An exhaustive presentation of the serosal origin of these lesions has recently been published by Lauche.[3] Irrespective of their

* From the Gynecological and Pathological Departments of the Albany Hospital and the Albany Medical College. Presented in part at the Forty-Ninth Annual Meeting of the American Gynecological Society, May 17, 1924.

1. Sampson, J. A.: Intestinal Adenomas of Endometrial Type, Arch. Surg. **5**:217-280 (Sept.) 1922; The Life History of Ovarian Hematomas (Hemorrhagic Cysts) of Endometrial (Müllerian) Type, Am. J. Obst. & Gynec. **4**:451-512 (Nov.) 1922; Benign and Malignant Endometrial Implants in the Peritoneal

Clinical/Pathological Criteria

SAMPSON, 1927

(1) coexistence of ca. and endometriosis within the same ovary
(2) similar histological pattern
(3) exclusion of a second malignant tumor elsewhere

Additional criterion **- Scott, 1953**

(4) demonstration of a histology-proven transition from benign endometriosis to ca.

Caso clinico

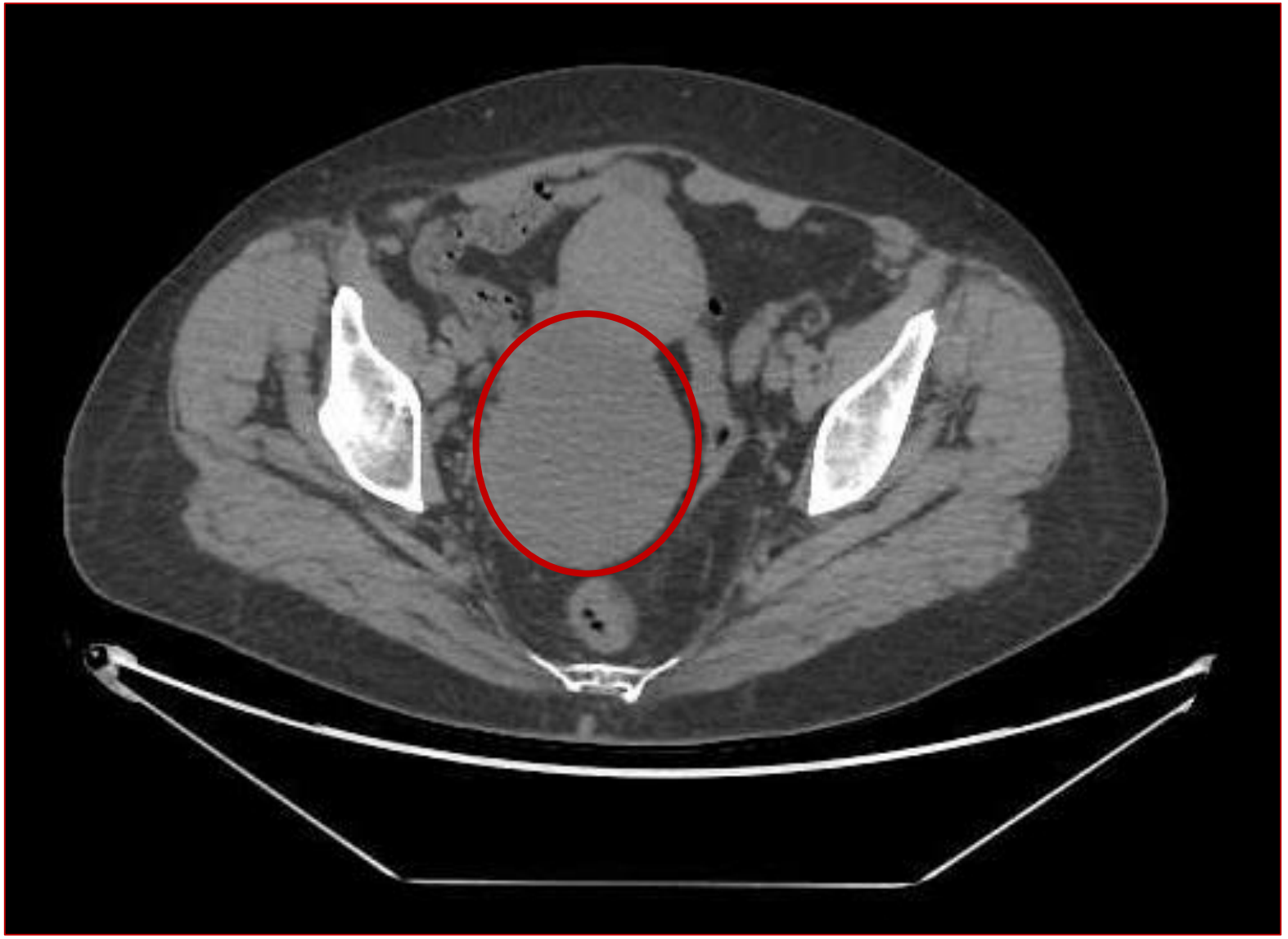
ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

- **A.F.S., 56aa, BMI 25.1**
- Familiarità onc. neg.
- Nulligravida, menopausa 52aa
- Ipertensione arteriosa in terapia medica
- Farmaco-allergia
- Pregresse miomectomie uterine (1 lpsc; 2 hsc)

- **APP:** seguita ecograficamente c/o altra ist. da circa 2aa (verosimile cisti endometriosica annex dx, diam. 5-6cm, senza segni di atipia, marcatori siero-onc. geg.)
- **Ecografia TV (9-4-19) INT-Na:** neoformazione annex dx (diam. circa 8cm, contenuto misto, centralmente denso e perifericamente solido con gettoni parietali senza segni di discontinuazione parietale)

- **CA125:** 15.8, **HE4:** 99 >>> **ROMA** 21.5 (v.n. postmenop. < 29.9)

- **TC addome-pelvi (23-4-19) INT-Na:** neoformazione pelvica similcistica mediana-paramediana dx, margini netti e regolari, contenuto omogeneo, verosimile pertinenza annex dx (7x8cm)



Chirurgia (30-4-19)

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

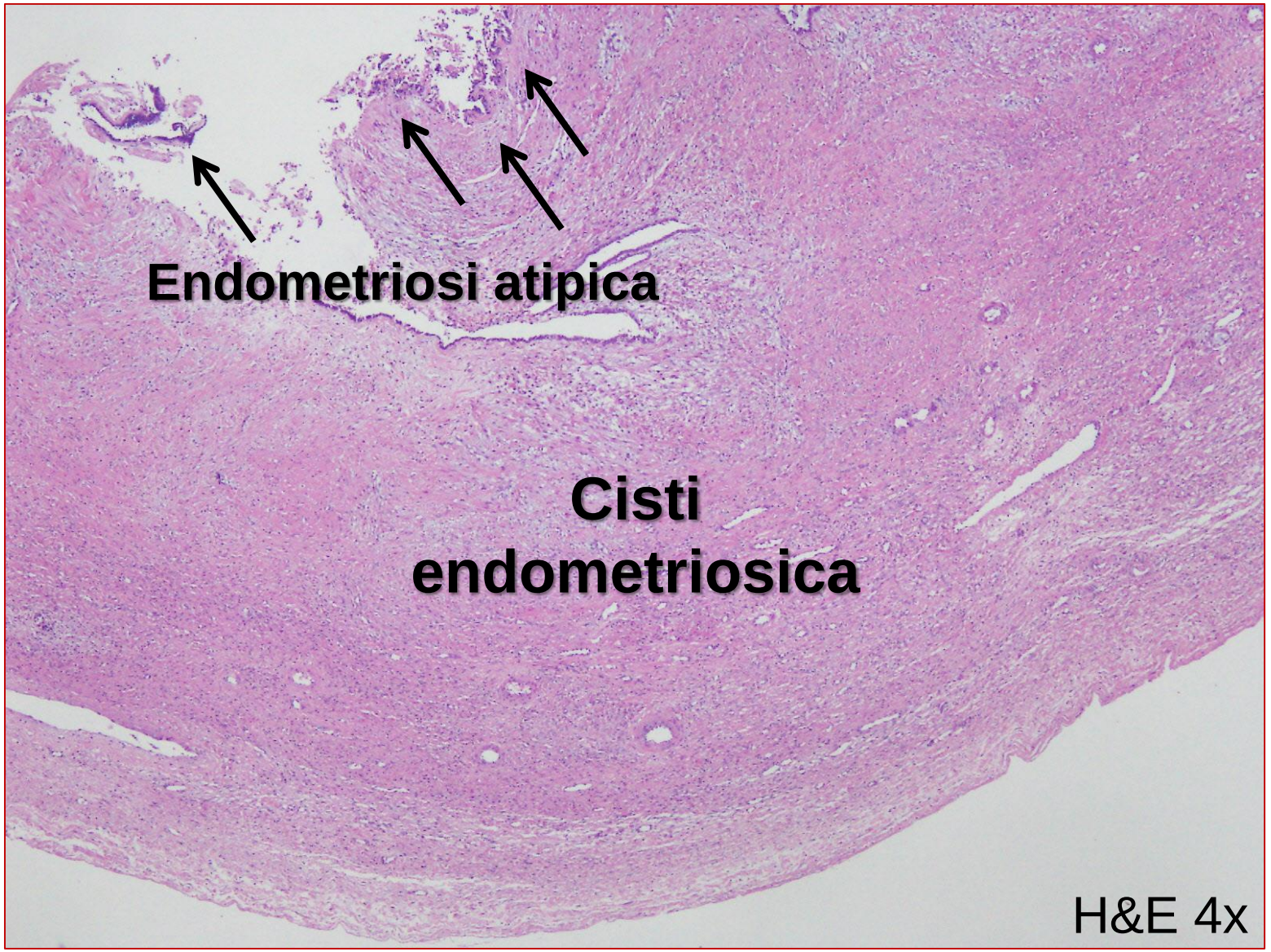
- **LPSC:** annex bilaterale (rottura cistoma in endobag), aspirazione liquido libero peritoneale

  Esame istologico al congelatore ovaio dx: ***carcinoma di alto grado***

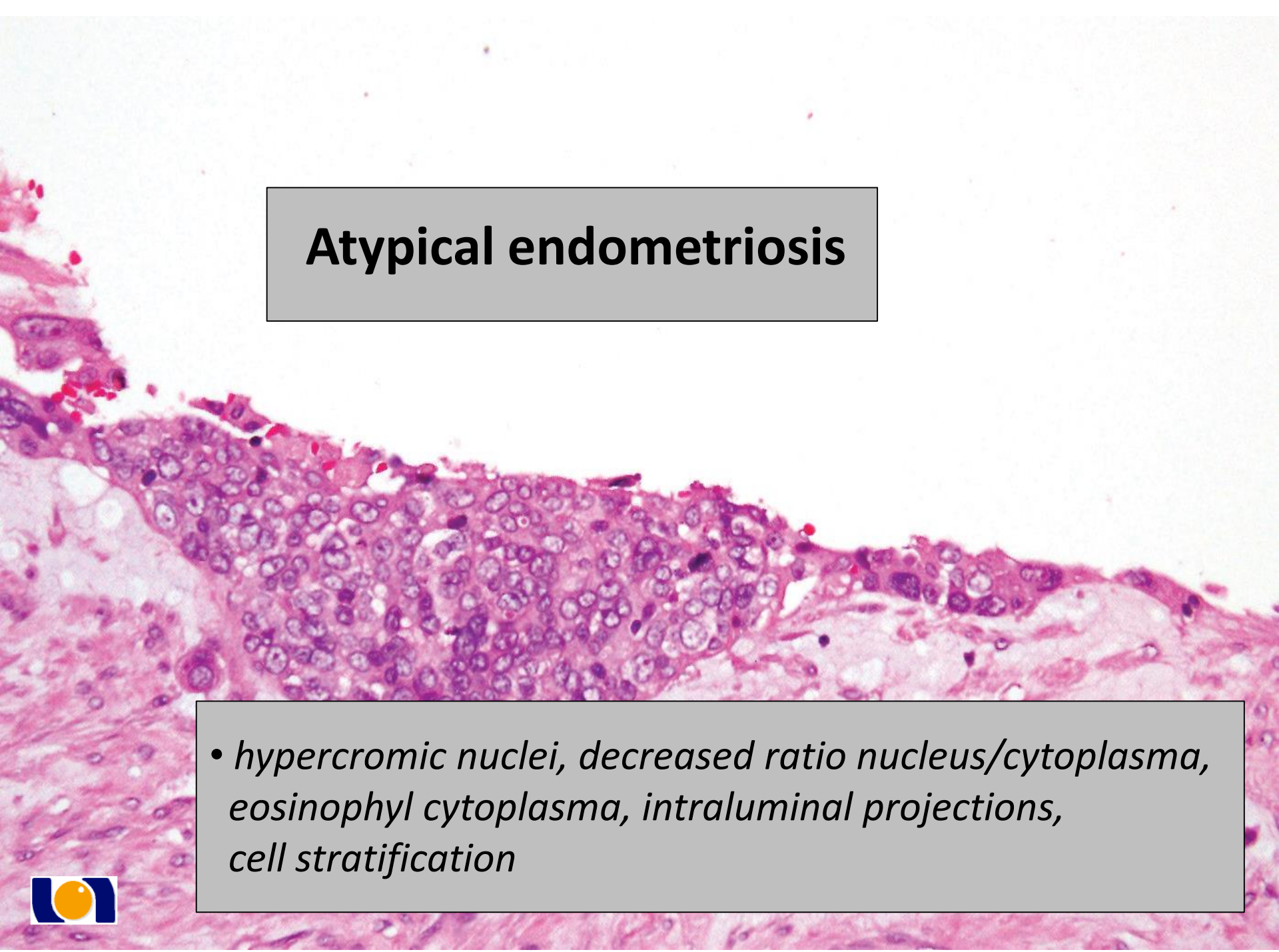
- **Conversione LPT:** isterectomia extrafasciale, omentectomia infracolica, linfoadenectomia aorto-pelvica

- **Esame istologico definitivo:** ***adenocarcinoma ovarico endometrioide scarsamente differenziato insorto su cisti endometriosica + cistoadenofibroma BL (ovaio dx)***
  focale iperplasia endometriale ghiand. semplice
  leiomiomi uterini multipli
  N aortici (neg 10/10), pelvici (neg. 14/14)
  Citologia peritoneale negativa

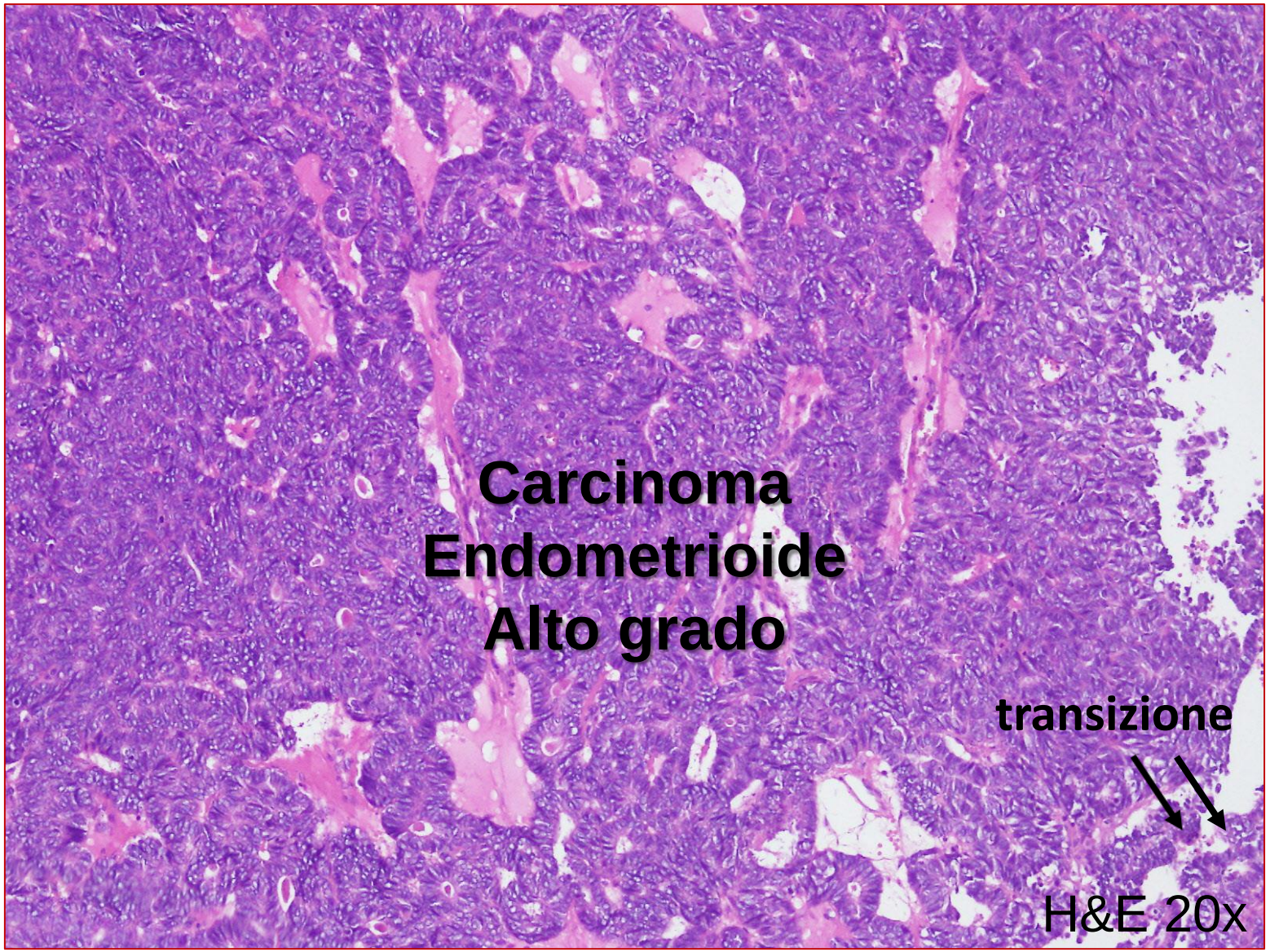
- **Stadio FIGO IC1-2** (rottura intraop./infiltrazione capsulare)


Endometriosi atipica
Cisti endometriosica
H&E 4x

Atypical endometriosis



- *hypercromic nuclei, decreased ratio nucleus/cytoplasma, eosinophyl cytoplasma, intraluminal projections, cell stratification*


Carcinoma
Endometrioide
Alto grado
transizione
H&E 20x

Endometriosis & OC
Open Questions

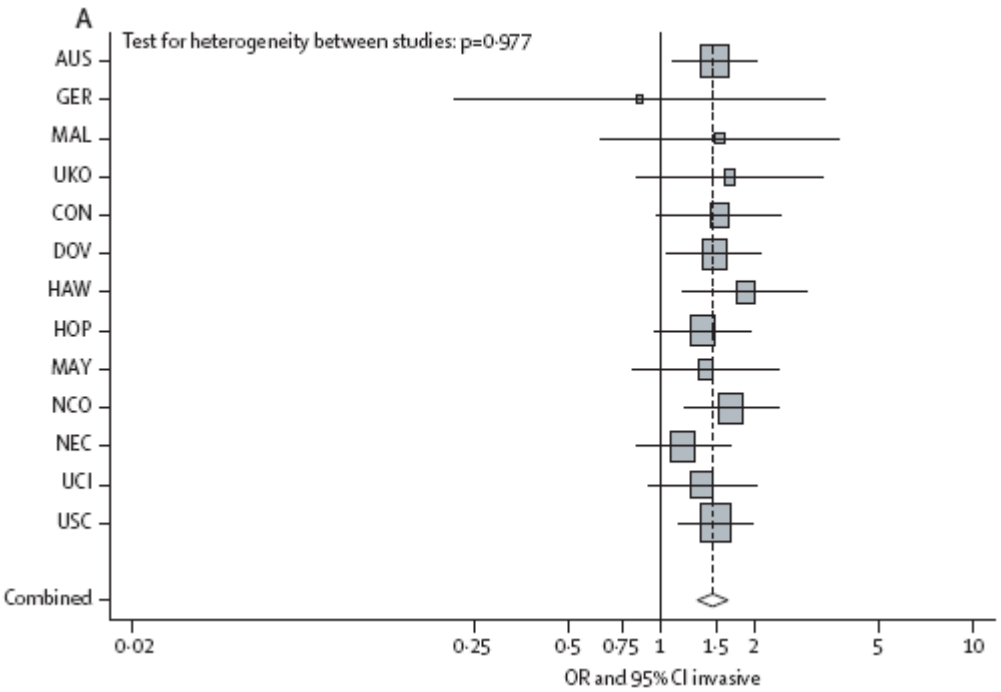
- Quantify the risk
- Clarify the pathways
- Endometriosis: premalignant lesion
- Type and prognosis of EAOC
- Management of (perimenopausal) pts with (history of) endometriomas

Association between Endometriosis and OC

OC Association Consortium

13 case-control studies

7911 Inv. Ocs
1907 BL OCs
13326 Controls



Invasive OC

OR 1.46, p<0.0001

Pearce, 2012

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

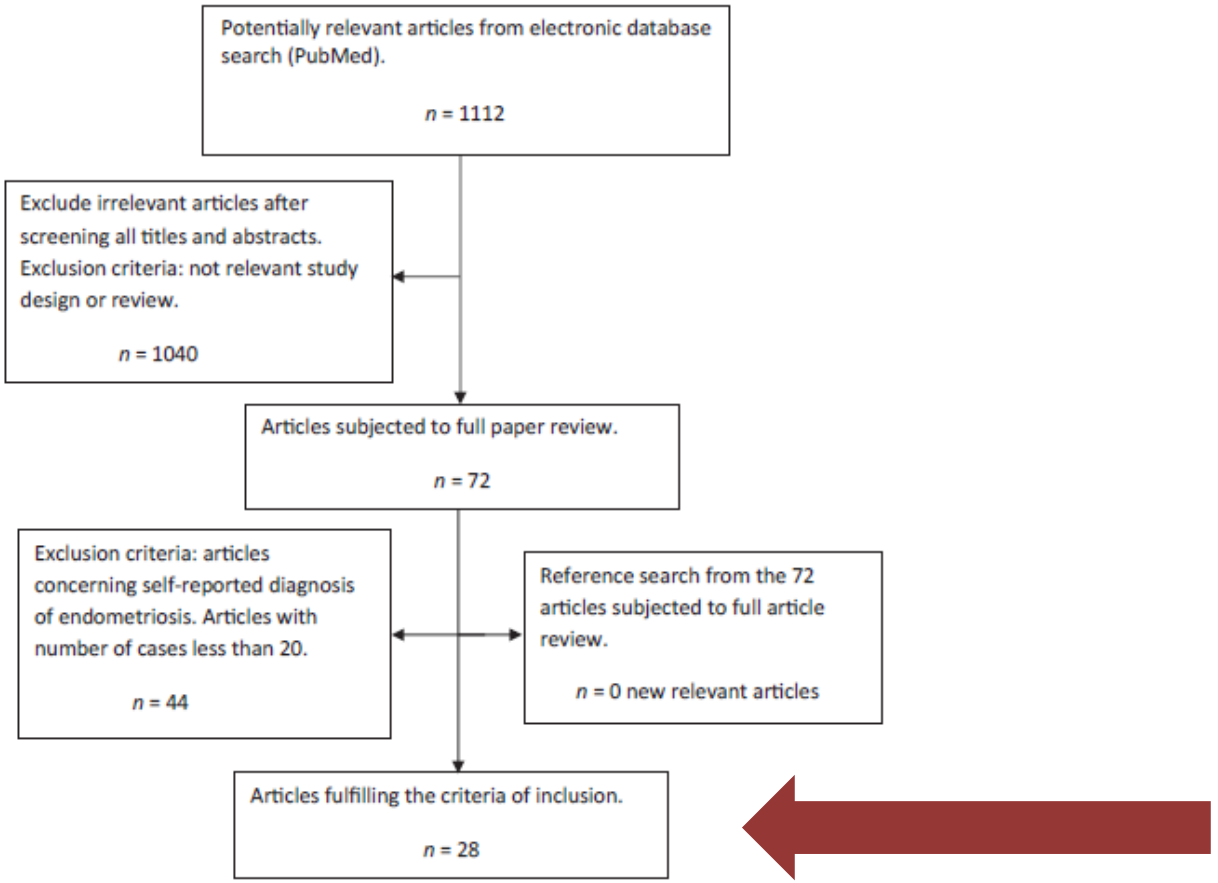
AOGS REVIEW ARTICLE

Acta Obstetricia et Gynecologica Scandinavica 93 (2014) 20–31

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



Endometriosis & OC

- ***Endometriosis in OC pts***
- Prevalence: 3.4-52.6%
- SIR: 2.48-3.75 (CI 1.3-4.2)

- ***OC in Endometriosis pts***
- Prevalence: 2.0-17%
- SIR: 1.43-8.95

Heidemann, 2014

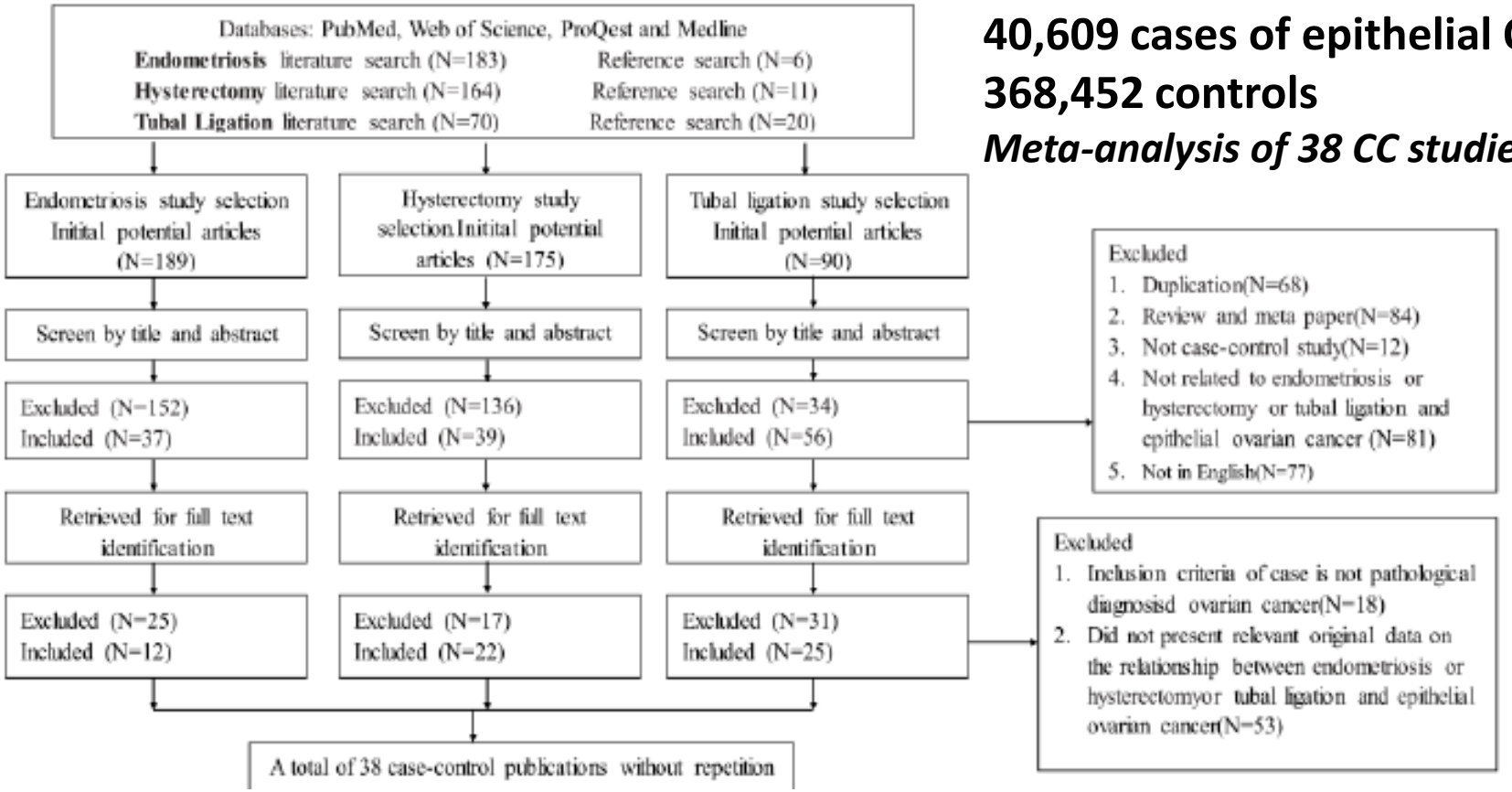
International Journal of *Environmental Research and Public Health*

Int. J. Environ. Res. Public Health **2016**, *13*, 1138;

Article

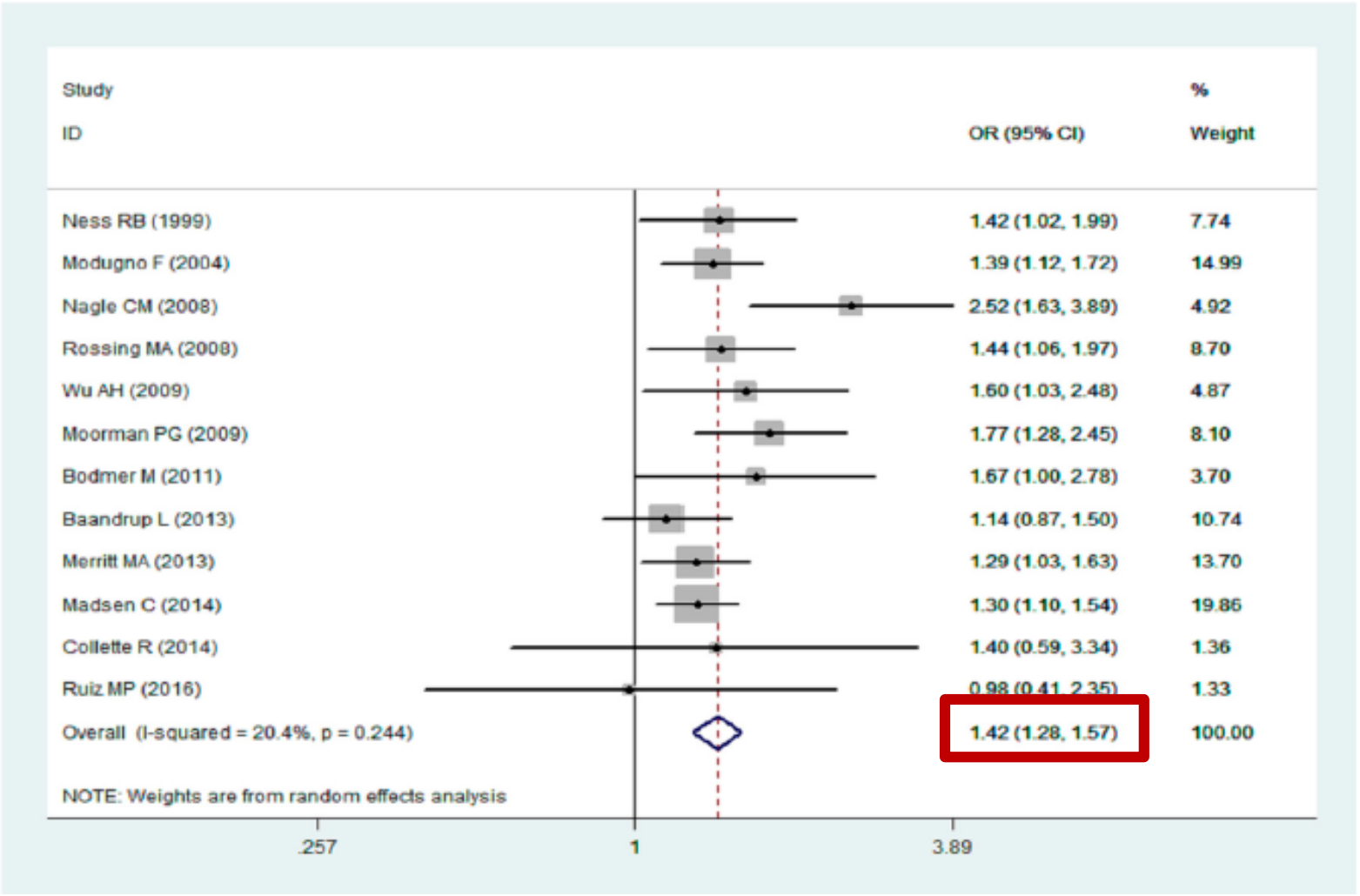
The Association between Endometriosis, Tubal Ligation, Hysterectomy and Epithelial Ovarian Cancer: Meta-Analyses

Chunpeng Wang [1,*], Zhenzhen Liang [2], Xin Liu [2], Qian Zhang [2] and Shuang Li [2]



40,609 cases of epithelial OC
368,452 controls
Meta-analysis of 38 CC studies

Association between Endometriosis and EOC



Gynecologic Oncology 143 (2016) 87–92

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study

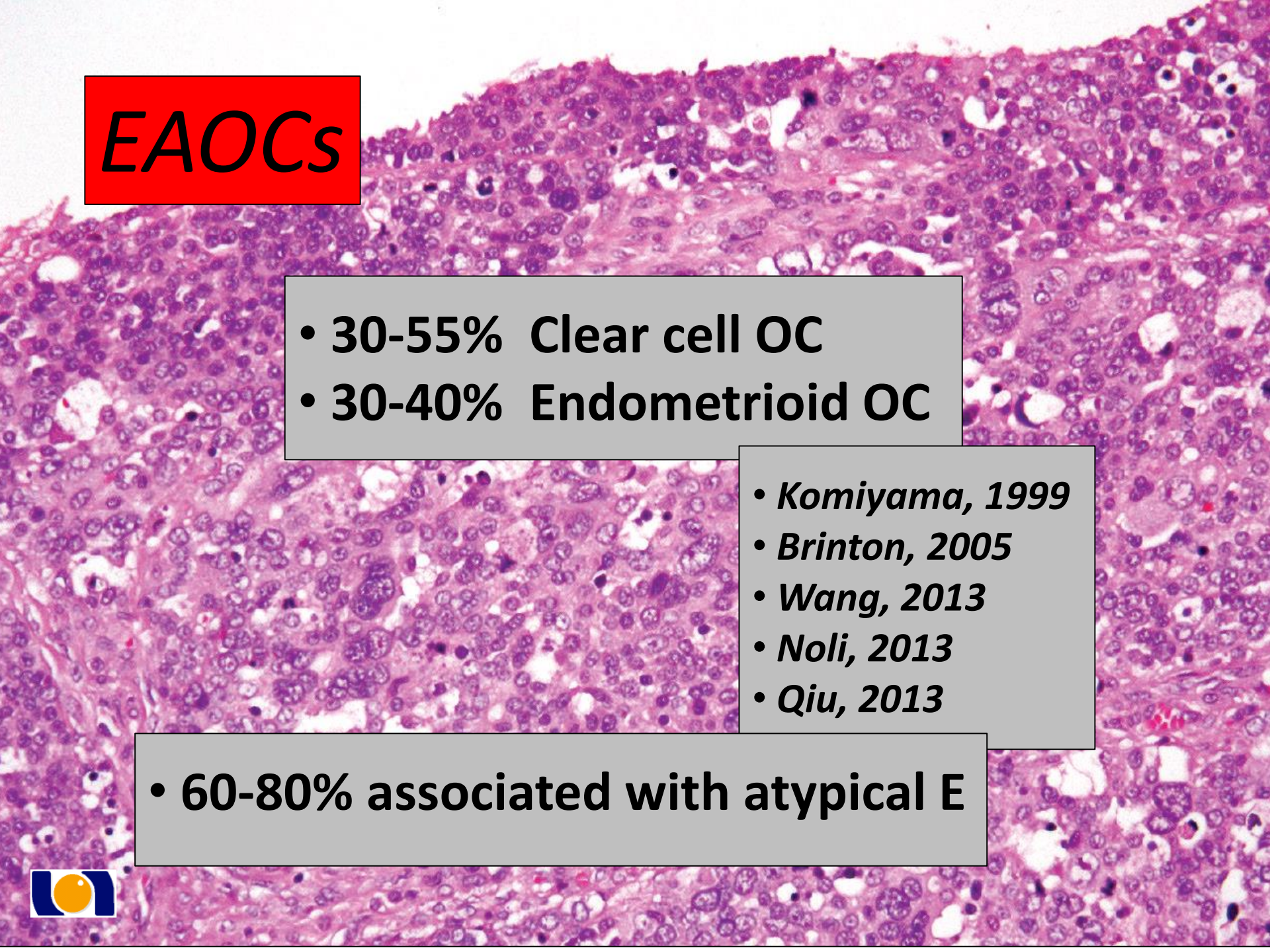
Julie Brøchner Mogensen [a], Susanne K. Kjær [a,b], Lene Mellemkjær [a], Allan Jensen [a,*]

[a] Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark
[b] Department of Gynaecology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

45.790 women with clin. diagnosis of endometriosis (1977-2012) linked with Danish Cancer Registry

Cancer site	Total follow-up					Follow up ≥1 year after first diagnosis of endometriosis				
	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)
Ovary	92,741	10.75 (0.26–29.33)	221	142.64	1.55 (1.35–1.77)	552,244	11.85 (2.11–29.07)	186	138.31	1.34 (1.16–1.55)
Endometrium	37,829	4.10 (0.01–22.73)	118	55.34	2.13 (1.77–2.55)	308,680	8.83 (1.35–25.86)	77	53.82	[illegible]
Breast	686,339	13.00 (2.53–30.22)	1452	1377.46	1.05 (1.00–1.11)	641,403	12.67 (2.34–29.42)	1397	1335.17	1.05 (0.99–1.10)

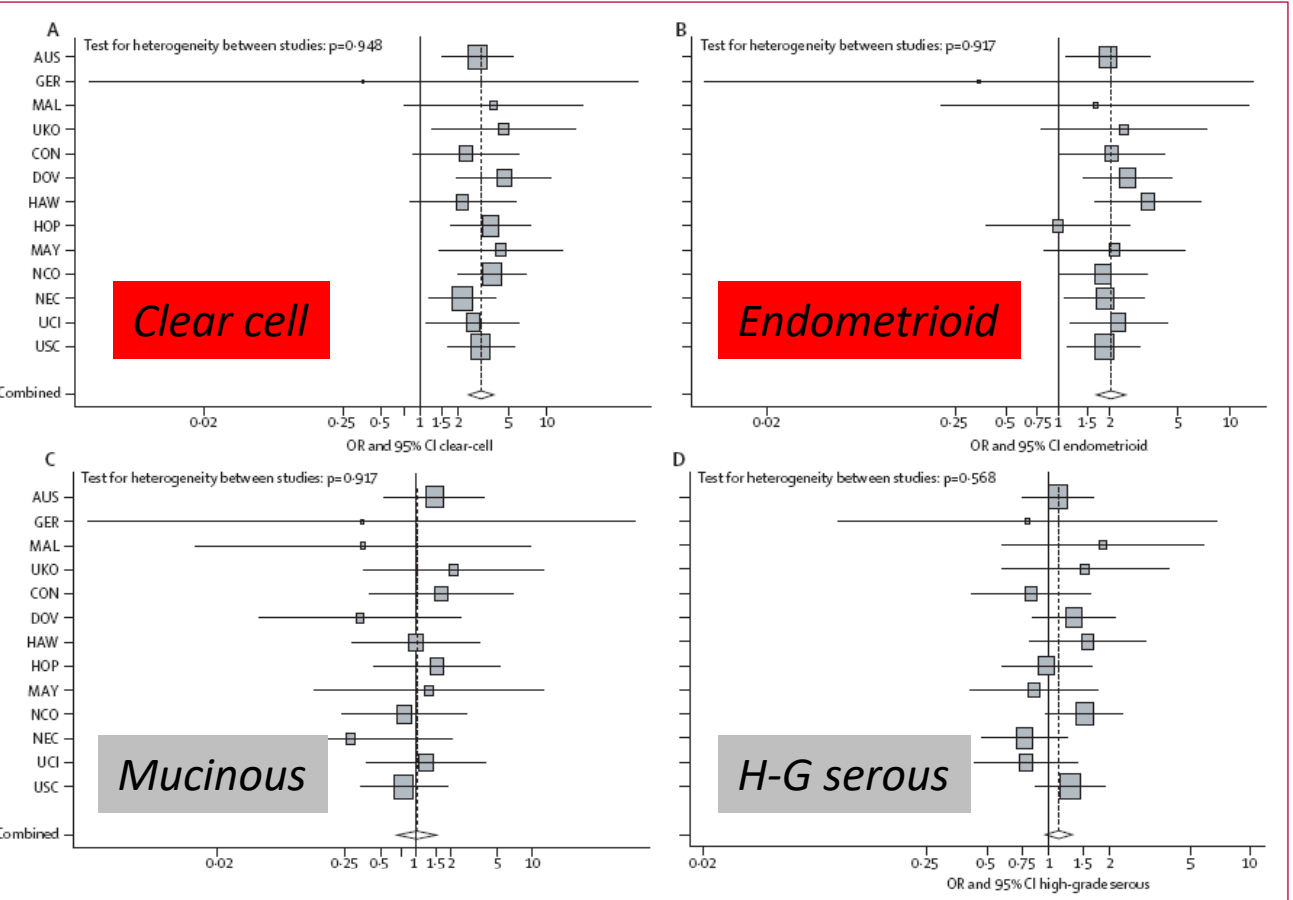
PY = person-years. MFU = median follow-up. P10 = 10th percentile. P90 = 90th percentile. O = observed. E = expected.


EAOCs
• 30-55% Clear cell OC
• 30-40% Endometrioid OC
• Komiyama, 1999
• Brinton, 2005
• Wang, 2013
• Noli, 2013
• Qiu, 2013
• 60-80% associated with atypical E

EAOC – *INT Naples (2005-2012)*

Histotype	N	*% Atypical Endometriosis*	*P*
Endometrioid	22	50	<.001
Clear cell	18	55.5	
Others	170	4.7	

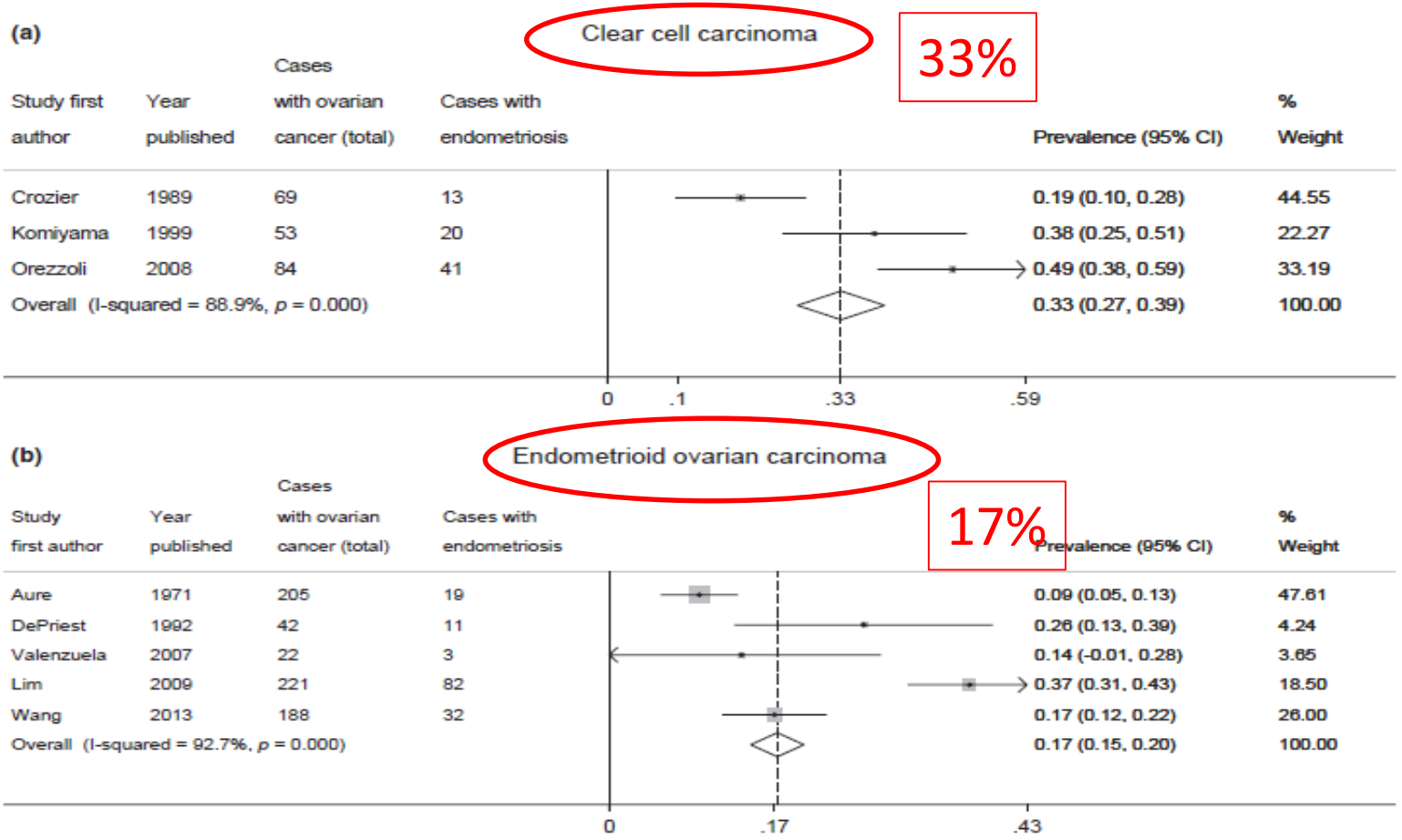
Greggi & Losito, 2013



Association between Endometriosis and OC Subtypes

Endometrioid….OR 2.04
p<.0001
Clear cell…….OR 3.03
p<.0001

Case-control studies meta-analysis – OC Ass. Consortium - Pearce, 2012



Prevalence by histological subtypes

Literature Meta-analysis - Heidemann, 2014

Nat. Cohort Study - *SIR for OC*

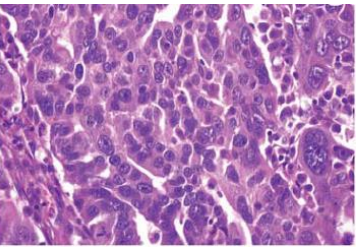
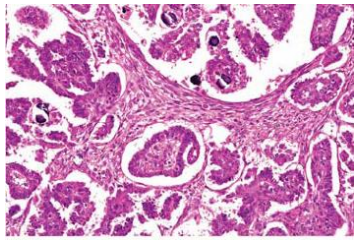
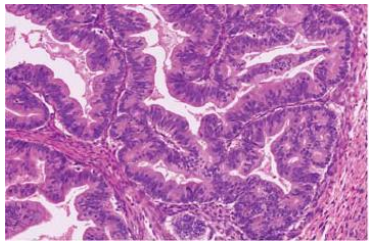
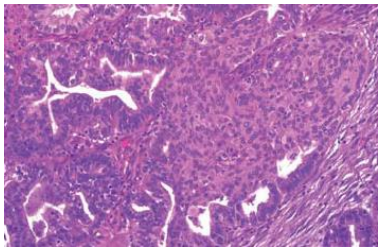
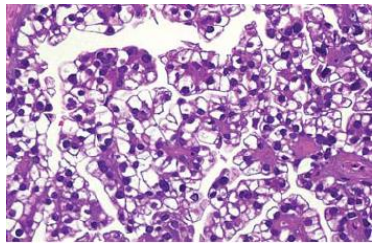
Histotype	SIR	95% CI
Serous	1.05	0.32-1.32
Mucinous	0.75	0.36-1.37
Endometrioid	**1.64**	1.09-2.37
Clear-cell	**3.64**	2.36-5.38

Mogensen, 2016

Kurman's dualistic theory

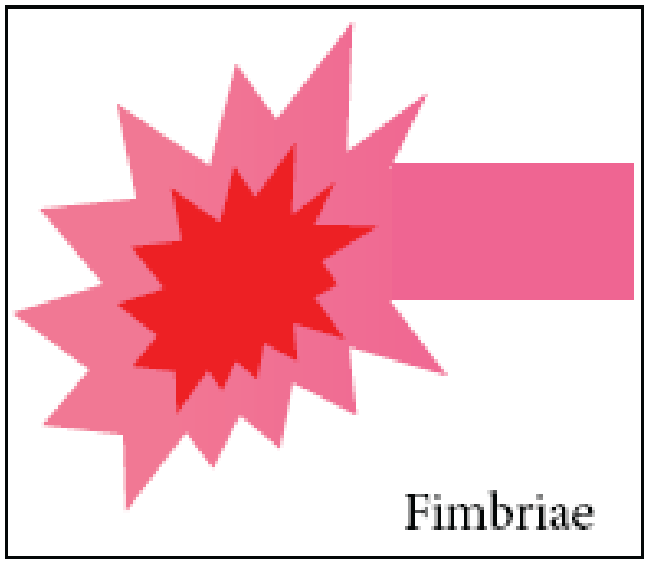
	Type I	Type II
Frequency (for the serous type)	25%	75%
Gene expression profile:		
BRAF mutations	30–65%	Low
K-RAS mutations	30–65%	Low
PTEN mutations	20%	Low
β catenin mutations	30%	Low
TP53 mutations	Low	50–80%
ARID1A mutation	40–50%	Not found
Genetic instability	+ (not very unstable)	+ (very unstable)
Microsatellite instability	50%	8–28%
HER2.neu overexpression	Low	20–67%
AKT overexpression	Low	12–30%
HLA-G overexpression	Low	61%
APO E overexpression	12%	66%
Ki67 proliferation index	10–15%	>50%
Cellular proliferation	Low	Strong
Stage	Stage I	>Stage I
Evolution	Slow	Fast
Survival rate at 5 years	55%	30%
Sensitivity to platinum salts (for the serous type)	Usually not very sensitive	Usually sensitive
Precursors	Sequence Cystadenoma/adenofibroma then borderline tumour	Probably de novo starting at the tubo-ovarian surface epithelium, dysplastic tubo-ovarian epithelium (STIL) and STICs
Histological type	Low-grade serous, mucinous, endometrioid, Clear cell carcinoma, Brenner's tumours	High-grade serous, Non-differentiated carcinoma, Carcinosarcoma

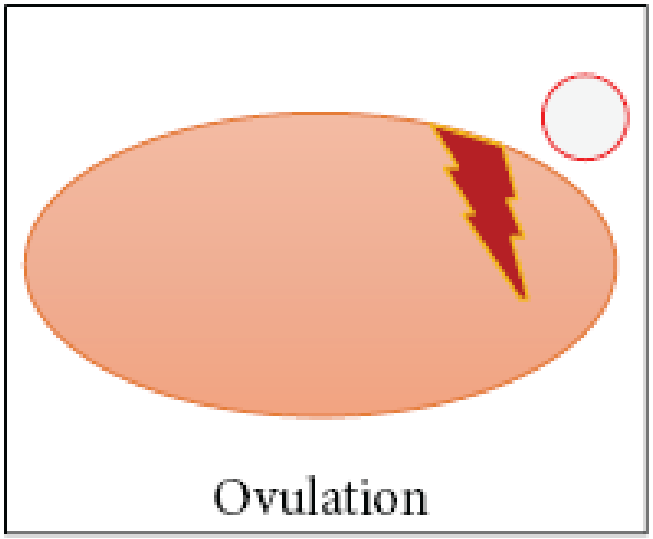
Clin. & Molecular Features of the 5 (most common) OC Types

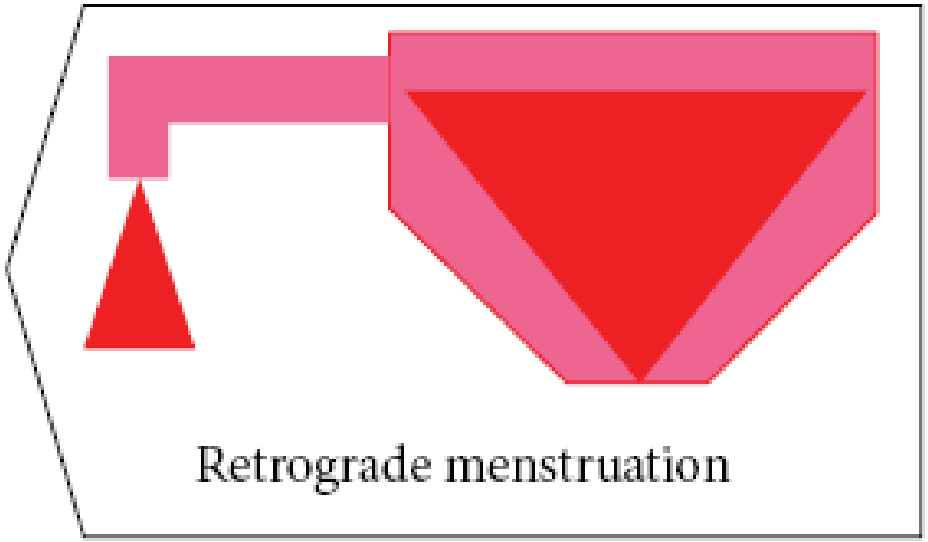
HG-Serous 70%	**LG-Serous <5%**	**Mucinous 3%**	**Endometrioid 10%**	**Clear cell 10%**
*BRCA*1/2	?	?	HNPCC	?
Tubal IP carcinoma	Serous Borderline ?	Cystadenoma Borderline ?	Atypical Endometriosis	Atypical Endometriosis
BRCA, p53	*BRAF, KRAS*	*KRAS, HER2*	*PTEN* (PI3K) *ARID1A* (BAF250) *CTNNB1* (Beta-cat)	*ARID1A* (BAF250) HNF1Beta
Progn. Poor	Intermediate	Favorable	Favorable	Intermediate

from Prat, 2012





Endometrioid, clear-cell
(serous?)



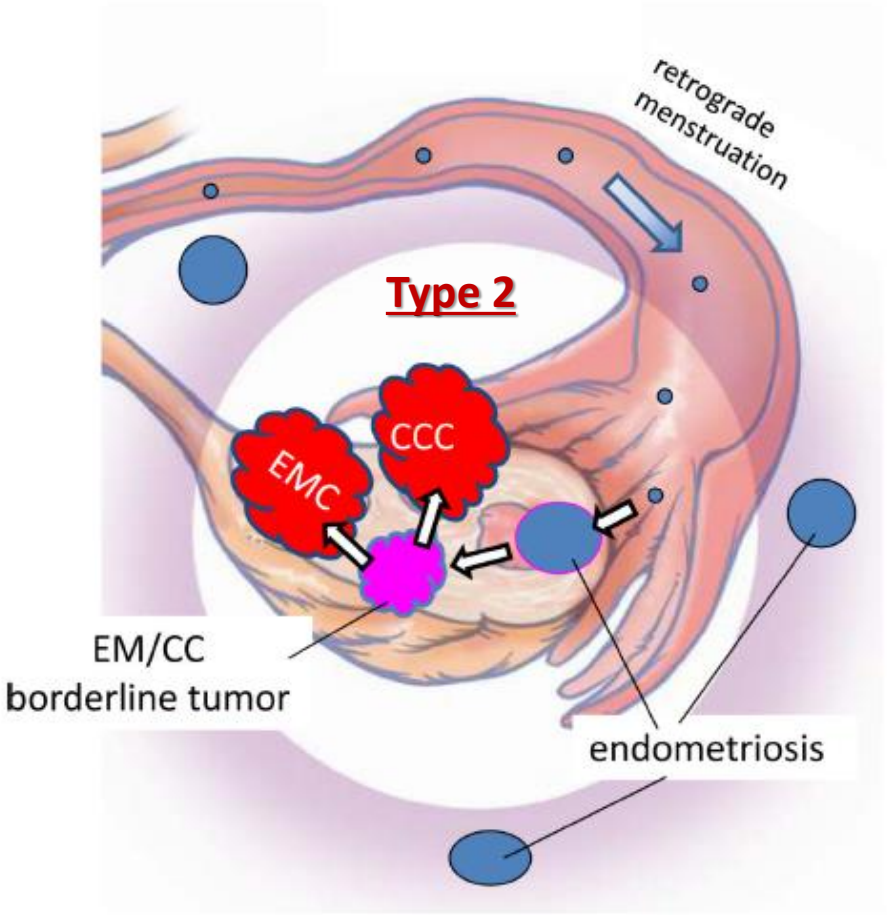
Endometrioid, clear-cell
(serous?)

The Origin and Pathogenesis of Epithelial Ovarian Cancer- a Proposed Unifying Theory

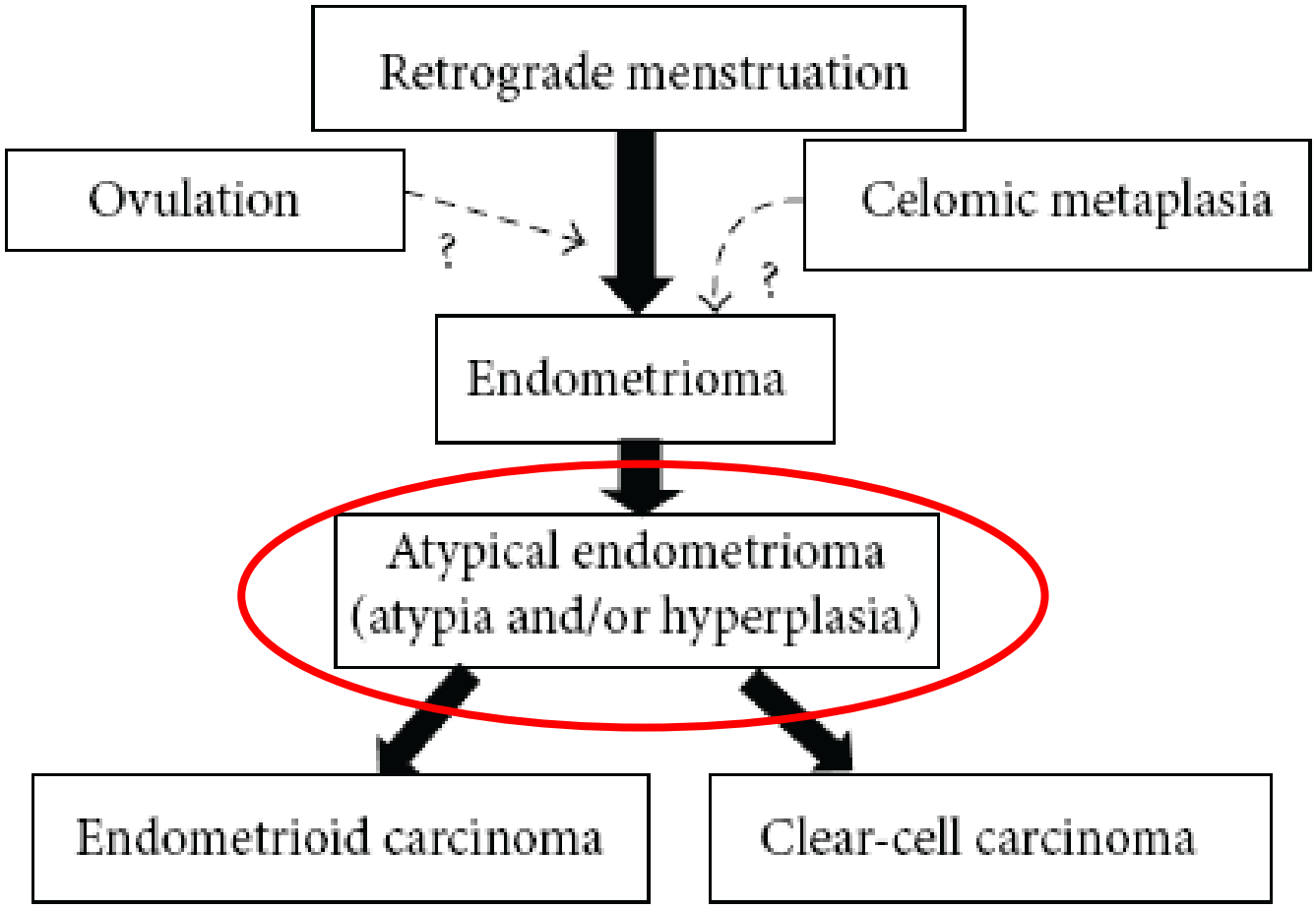
Robert J. Kurman, M.D. and **Ie-Ming Shih, M.D., Ph.D.**
Departments of Pathology, Gynecology and Obstetrics and Oncology The Johns Hopkins University School of Medicine, Baltimore, Maryland

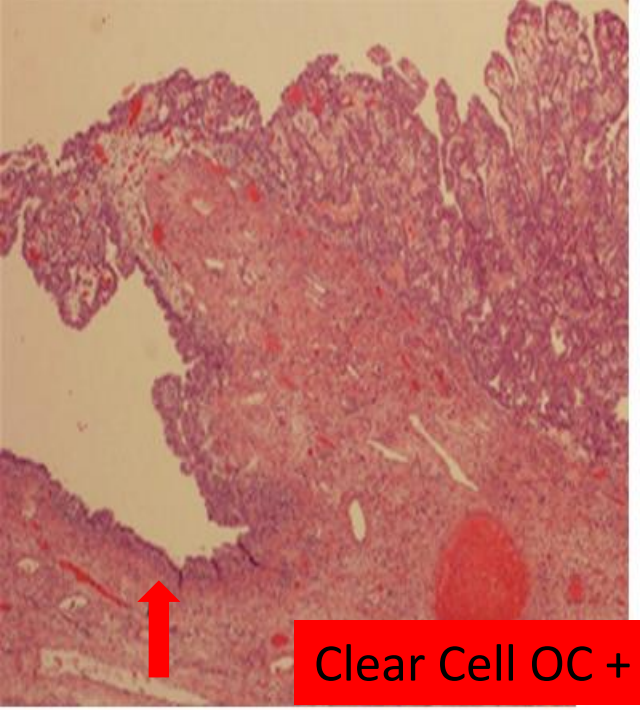
- Endometrial tissue, by a process of retrograde menstruation, implants on the ovarian surface to form an **endometriotic cyst** from which an **EMC** or **CCC** can develop

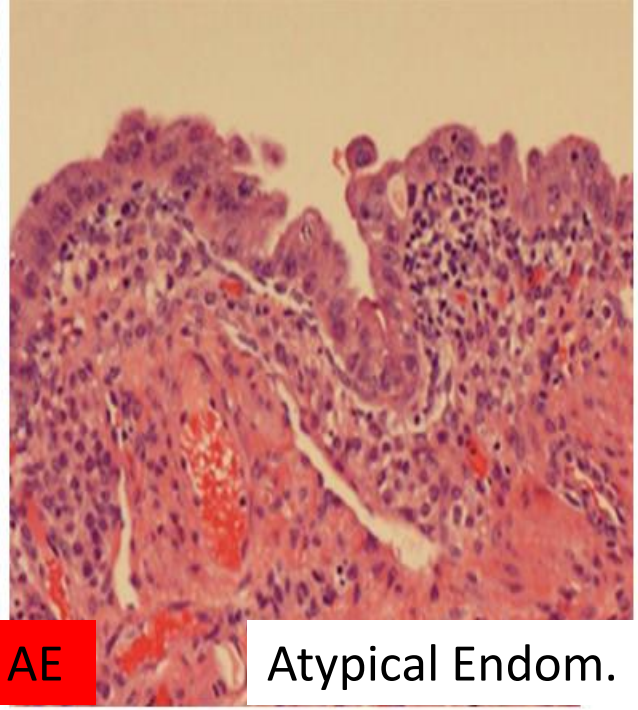
- **EMC: endometrioid ca. of the ovary**
- **CCC: clear cell ca. of the ovary**

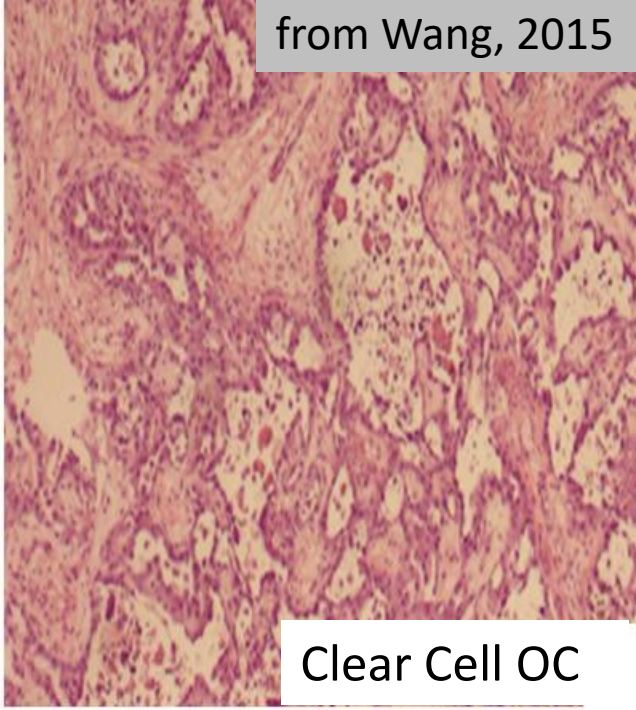


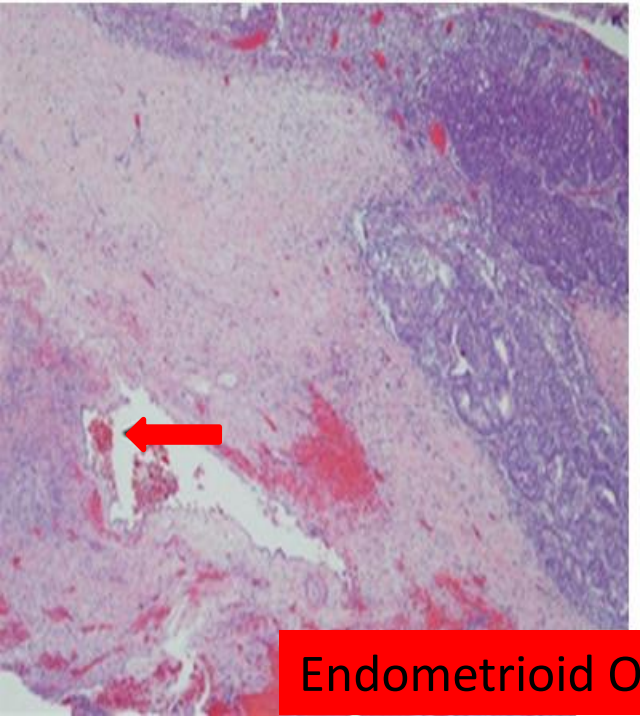
Proposed step-by-step process of transformation

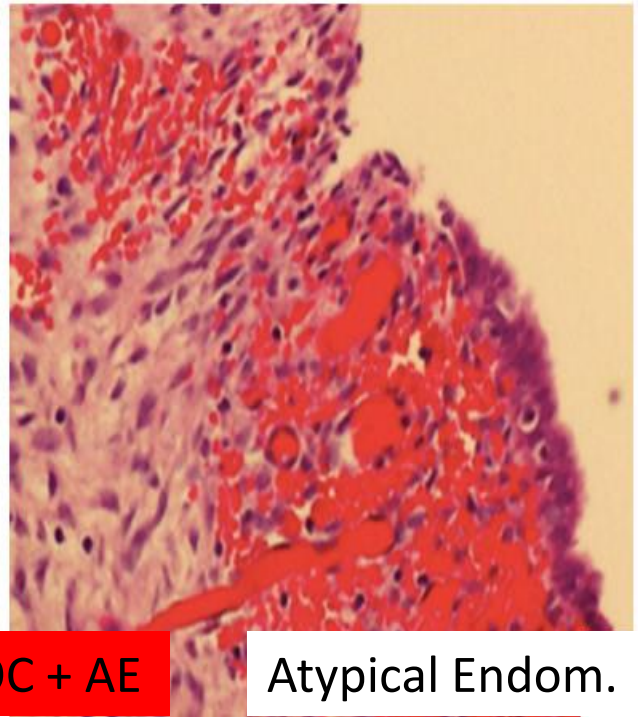


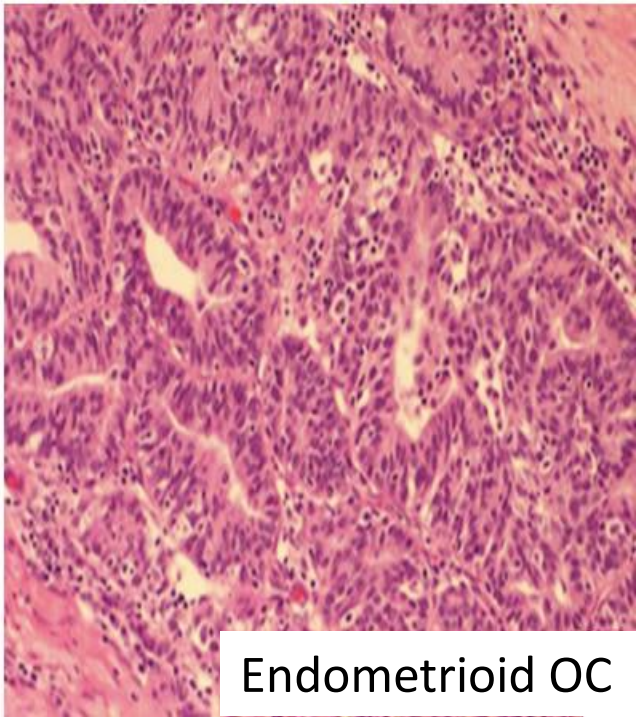

Clear Cell OC + AE

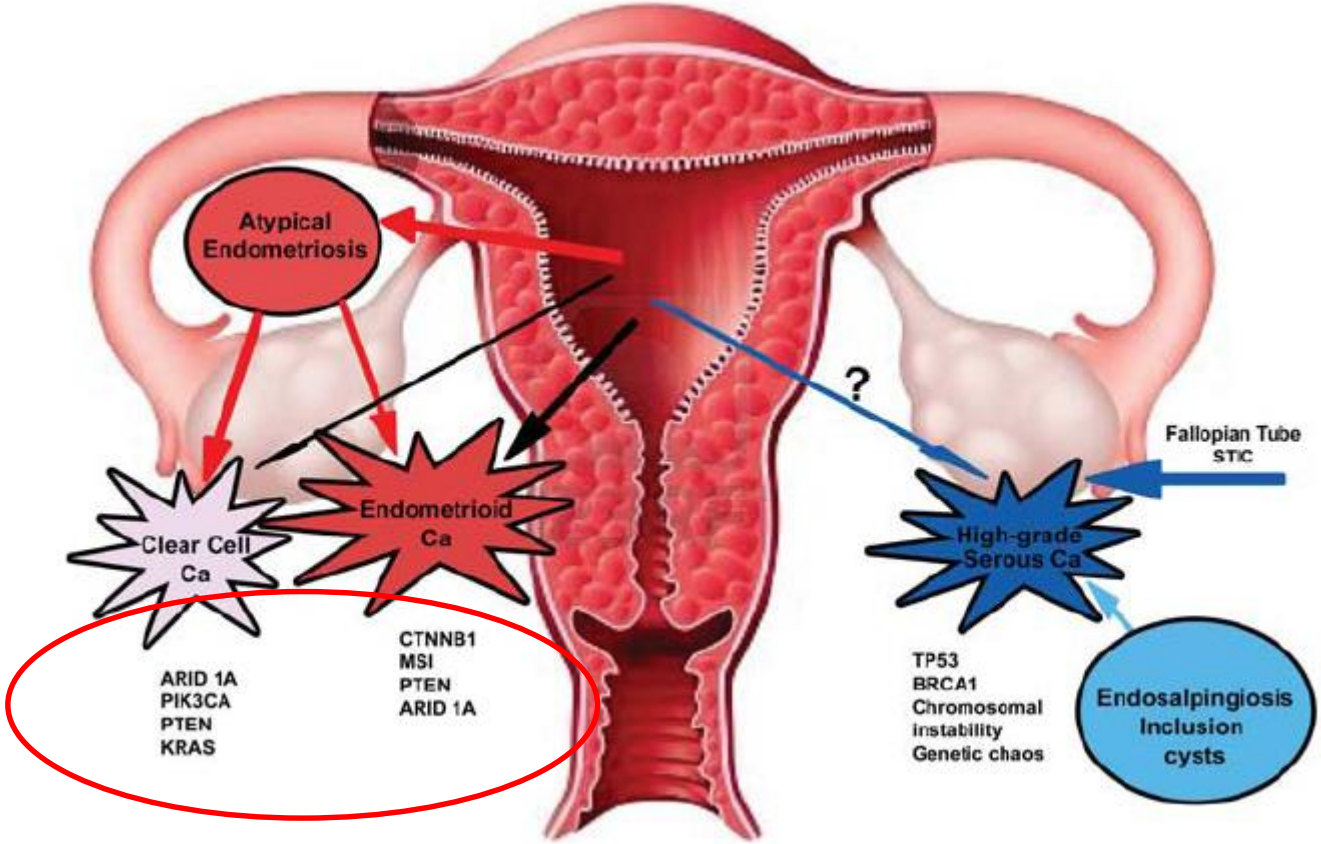

Atypical Endom.


from Wang, 2015
Clear Cell OC


Endometrioid OC + AE

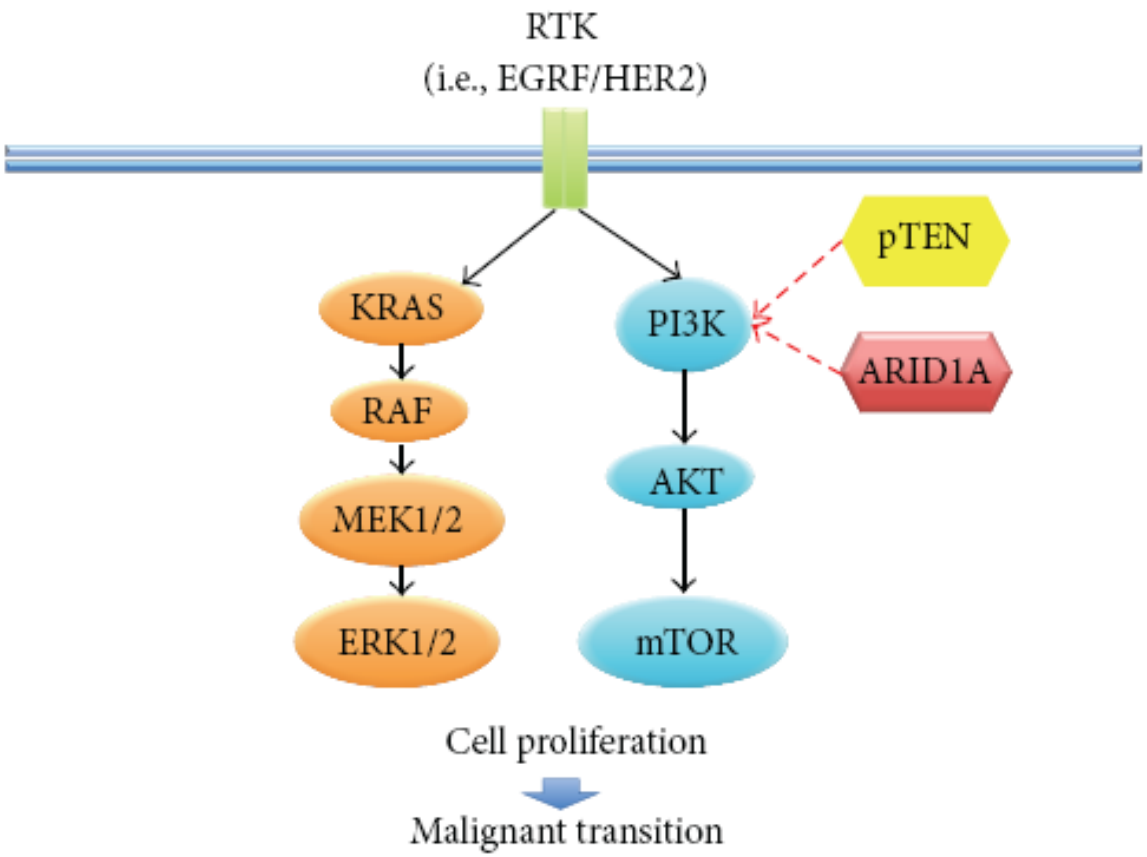

Atypical Endom.


Endometrioid OC



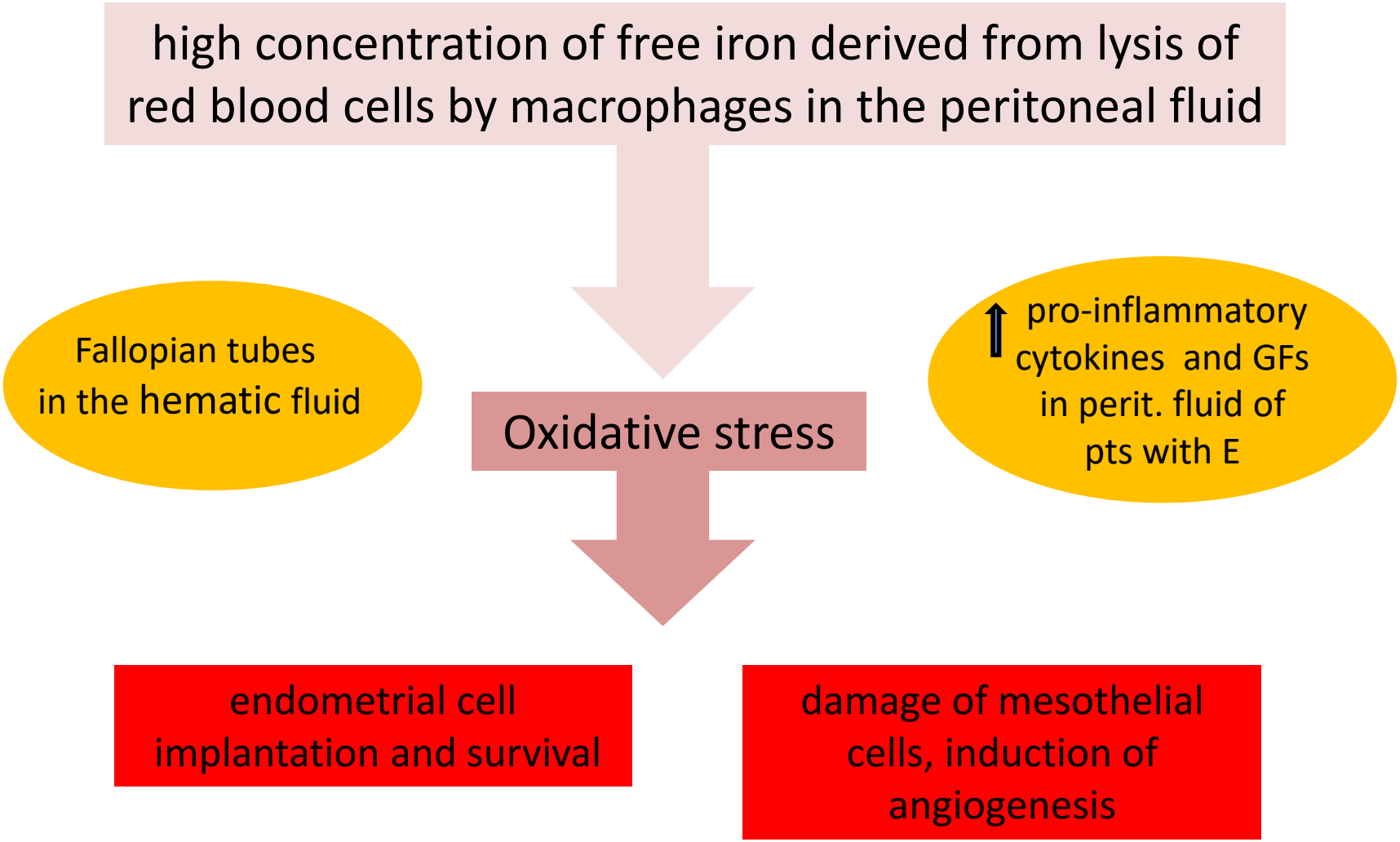
from Prat, 2012

Molecular pathways in EAOC from endometriotic lesions



Activation of oncogenes KRAS and PI3K
Inactivation of T-suppressor genes PTEN and ARID1A

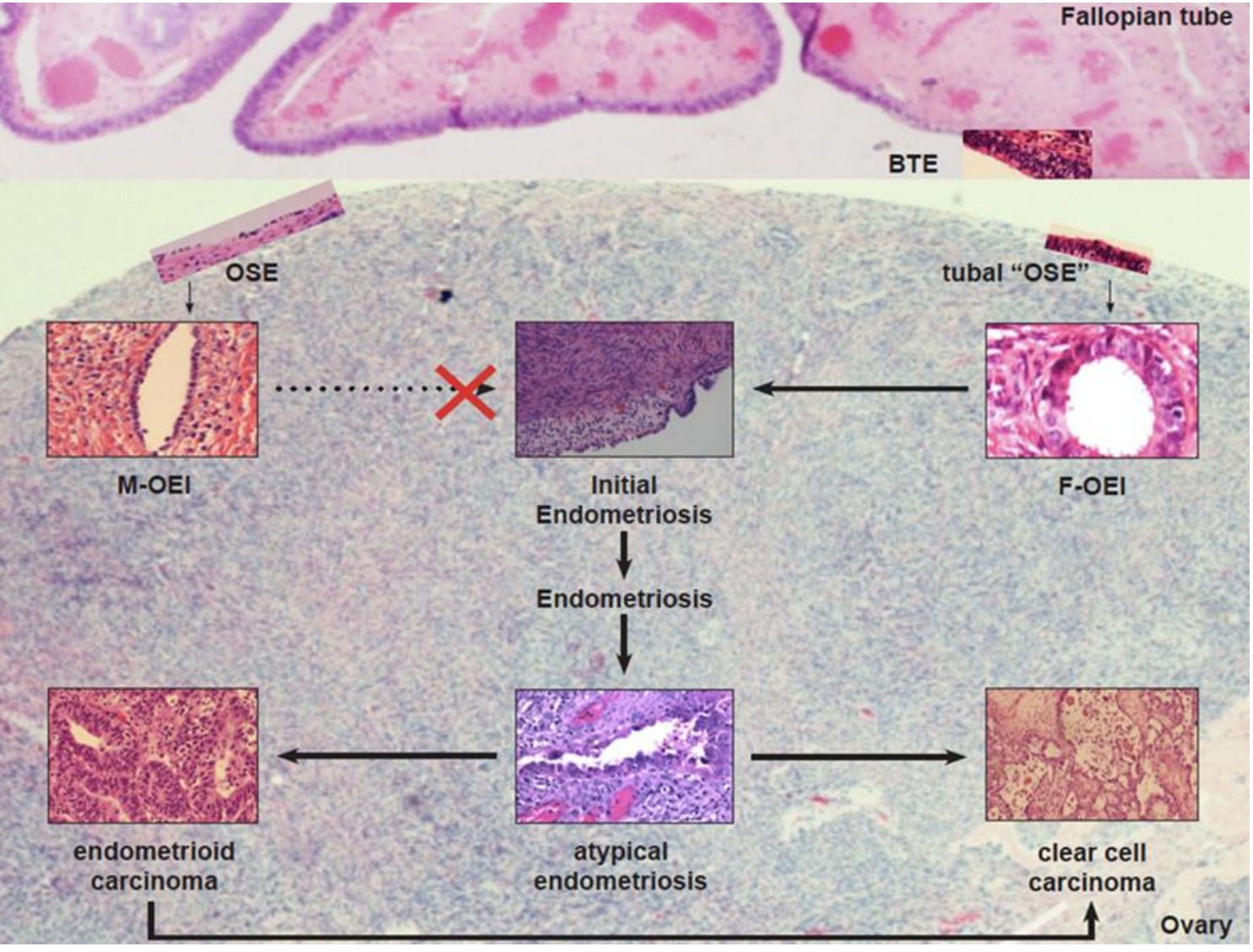
***ARID1A**:* gene encoding proteins (BAF250a) involved in chromatin remodeling , identified as a tumor suppressor gene; mutations found in atypical endometriosis


high concentration of free iron derived from lysis of red blood cells by macrophages in the peritoneal fluid
Fallopian tubes in the hematic fluid
Oxidative stress
pro-inflammatory cytokines and GFs in perit. fluid of pts with E
endometrial cell implantation and survival
damage of mesothelial cells, induction of angiogenesis

phenotypically normal endometrial cells
displaced into the pelvis by retrograde menstrual flow
develop the adhesive and proliferative properties of endometriosis

over time, these cells acquire the mutations
and become invasive OC

Proposed model of the development of clear cell and endometrioid OC from tubal-derived endometriosis



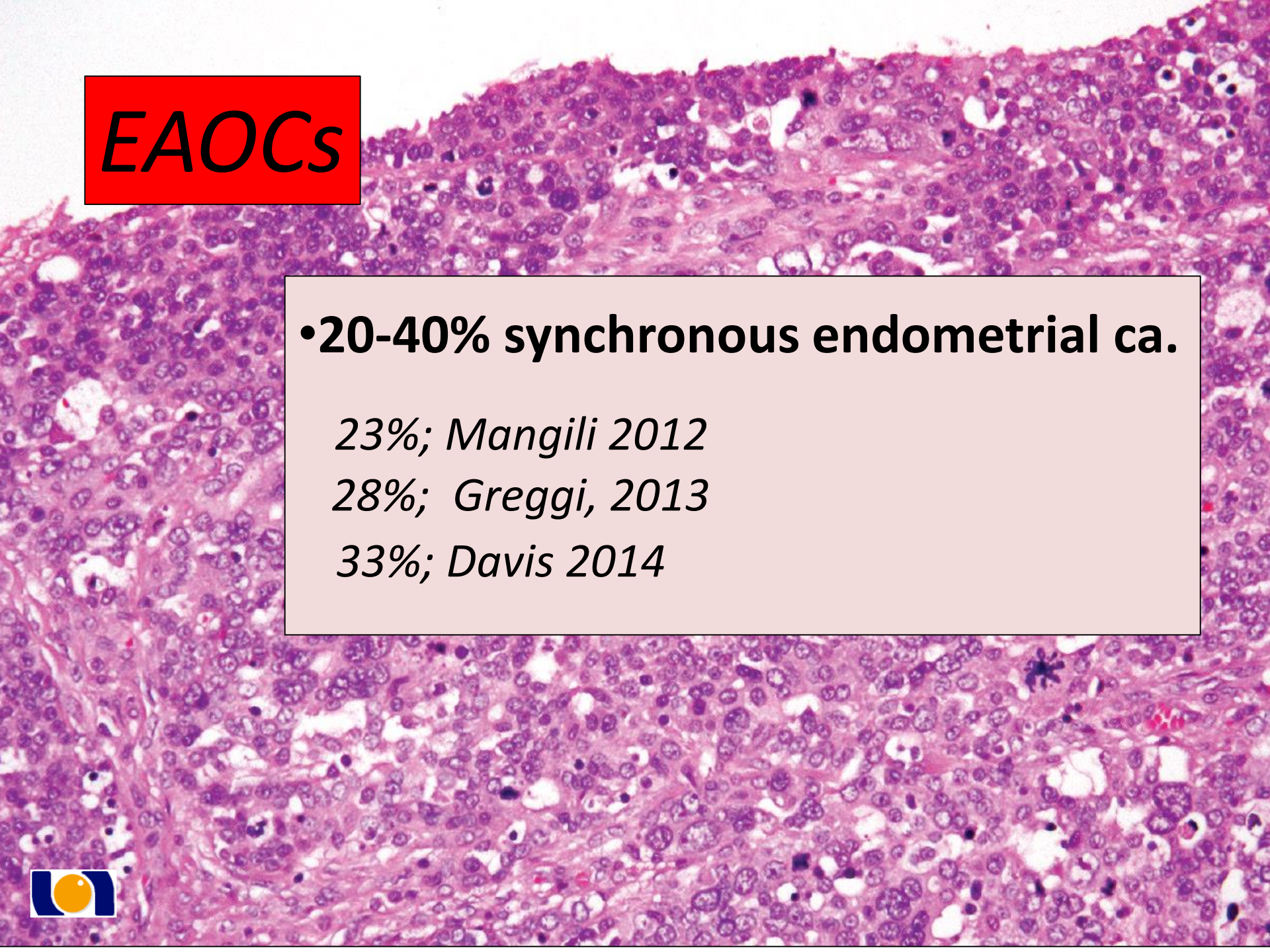
BTE: benign tubal epithelium
OSE: ov. surface epithelium
OEI: ov. epithelial inclusions
M-OEI: mesothel. derived
F-OEI: Fallop. Tube derived

from Wang, 2015

the inciting event is the ***mutation in eutopic endometrium*** that allows for endometrial cell migration through the fallopian tubes and proliferation outside of the uterus

invasive endometriosis phenotype and subsequent ca.

molecular differences originally thought to be isolated to endometriotic tissue, were found also in eutopic endometrial tissue of women with endometriosis and absent in endometrial tissue of disease-free women


EAOCs
•20-40% synchronous endometrial ca.
23%; Mangili 2012
28%; Greggi, 2013
33%; Davis 2014

Gynecologic Oncology 143 (2016) 87–92

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study

Julie Brøchner Mogensen [a], Susanne K. Kjær [a,b], Lene Mellemkjær [a], Allan Jensen [a,*]

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[b] Department of Gynaecology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

45.790 women with clin. diagnosis of endometriosis (1977-2012) linked with Danish Cancer Registry

Cancer site	Total follow-up					Follow up ≥1 year after first diagnosis of endometriosis				
	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)
Ovary	92,741	10.75 (0.26–29.33)	221	142.64	1.55 (1.35–1.77)	552,244	11.85 (2.11–29.07)	186	138.31	1.34 (1.16–1.55)
Endometrium	37,829	4.10 (0.01–22.73)	118	55.34	2.13 (1.77–2.55)	308,680	8.83 (1.35–25.86)	77	53.82	1.43 (1.13–1.79)
Breast	686,339	13.00 (2.53–30.22)	1452	1377.46	1.05 (1.00–1.11)	641,403	12.67 (2.34–29.42)	1397	1335.17	1.05 (0.99–1.10)

PY = person-years. MFU = median follow-up. P10 = 10th percentile. P90 = 90th percentile. O = observed. E = expected.

Critical Reviews in Oncology / Hematology 134 (2019) 72–81

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

The risk of extra-ovarian malignancies among women with endometriosis: A systematic literature review and meta-analysis

S. Gandini[a], M. Lazzeroni[b], F.A. Peccatori[c], B. Bendinelli[d], C. Saieva[d], D. Palli[d], G. Masala[d], S. Caini[d,*]

32 studies published between 1989 and 2018

Increased risk

- Endometrial cancer (SRR 1.38, 95%CI 1.10–1.74)

No association

- Breast cancer (SRR 1.04, 95%CI 0.99–1.09)
- Melanoma (SRR 1.31, 95%CI 0.86–1.96)

Inverse association

- Cervical cancer (SRR 0.78, 95%CI 0.60–0.95)

SRR: summary relative risk

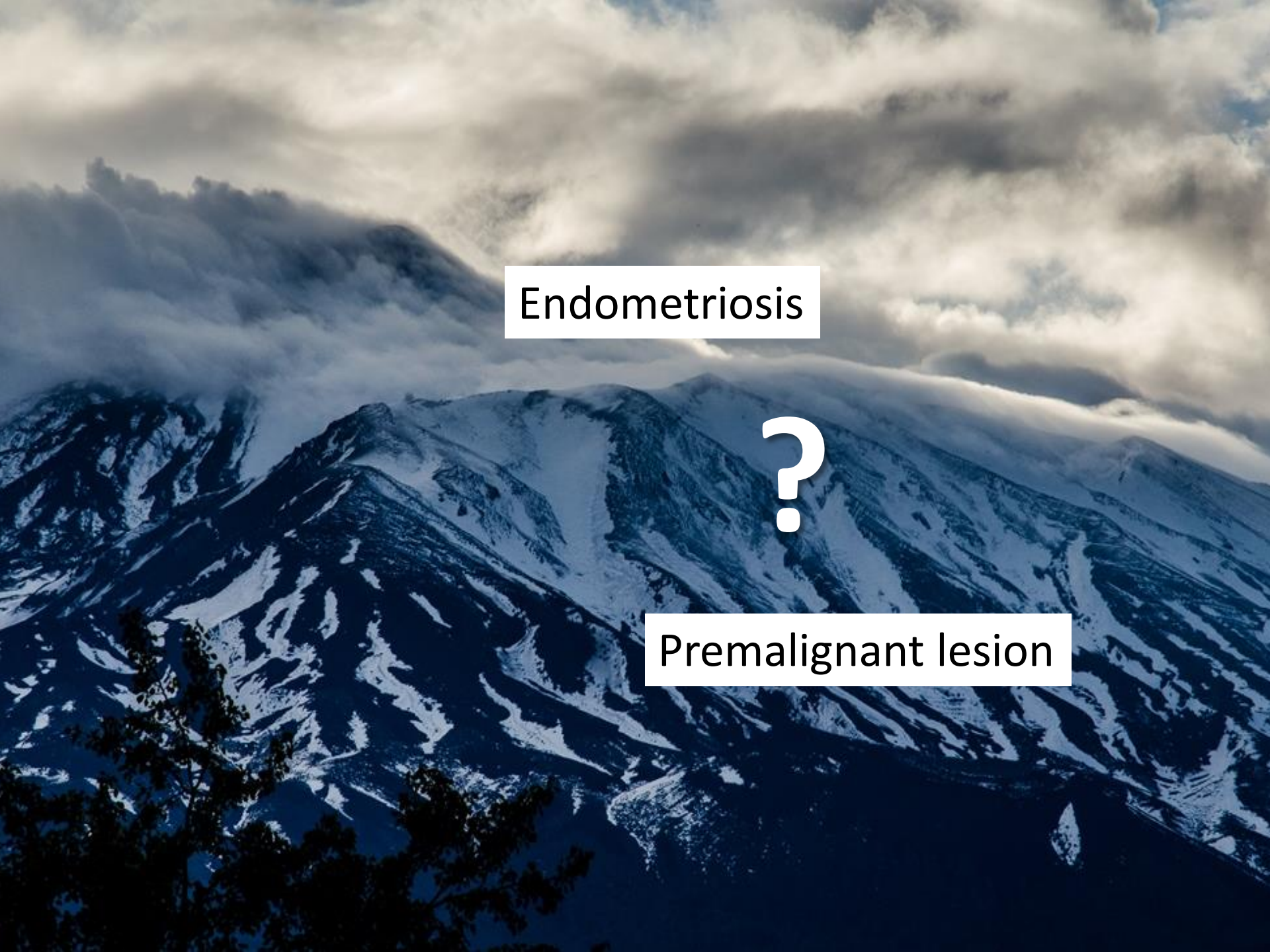
Table 3

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for specific histotypes of ovarian, endometrial and breast cancer among Danish women with endometriosis diagnosed in 1977–2012. Cancers and person–years in the first year after a diagnosis of endometriosis were excluded.

Histotype of cancer	O	E	SIR (95% CI)
Ovarian			
Serous	70	66.80	1.05 (0.82–1.32)
Mucinous	10	13.41	0.75 (0.36–1.37)
Endometrioid	28	17.09	1.64 (1.09–2.37)
Clear-cell	25	6.87	3.64 (2.36–5.38)
Endometrial			
Type 1	67	43.41	1.54 (1.20–1.96)
Type 2	4	3.78	1.06 (0.28–2.71)
Breast			
Ductal	1034	997.28	1.04 (0.97–1.10)
Lobular	176	153.82	1.14 (0.98–1.33)

O = observed. E = expected.

Nat. Cohort Study - Mogensen, 2016


Endometriosis
?
Premalignant lesion

NCI –GW Univ. Consensus Conf. on «Precancer», 2014

- *Precancer* with increased risk of cancer
- Cancer arising from cells within the *precancer*
- *Precancer* different from tissue of origin
- *Precancer* different from cancer (some, but not all mol./phenotypic characteristics)
- *Precancer* can be diagnosed

NCI –GW Univ. Consensus Conf. on «Precancer», 2014

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- *Precancer* different from tissue of origin
- *Precancer* different from cancer (some, but not all mol./phenotypic characteristics)
- *Precancer* can be diagnosed

E – *Premalignant lesion?*

Eutopic endometrium → *precursor site of origin*

Endometriosis → *potential precursor*

Atypical endometriosis → *immediate precursor*

Kurman, 2016

Identification of Precancer

(E cysts with atypical endometriosis)

Method of Precancer Diagnosis

Hystopathological only ?

Functional imaging

Mol. analysis of biol. samples

Clinical (USS) Characteristics

- **Typical**

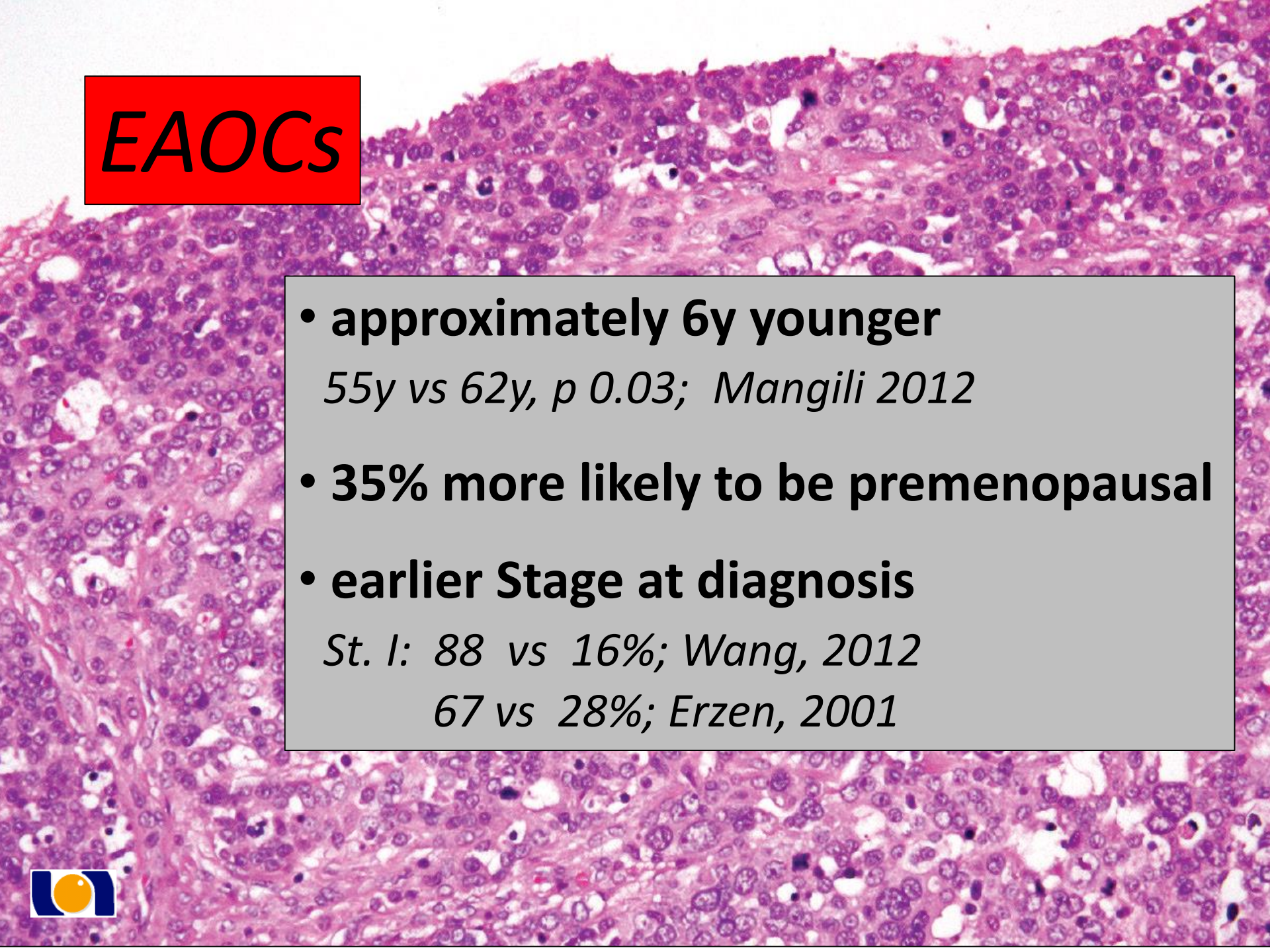
(Premenop.)

- Unilocular
- Multiloc. (<4)
- Ground glass echogen.
- No solid parts/papill.

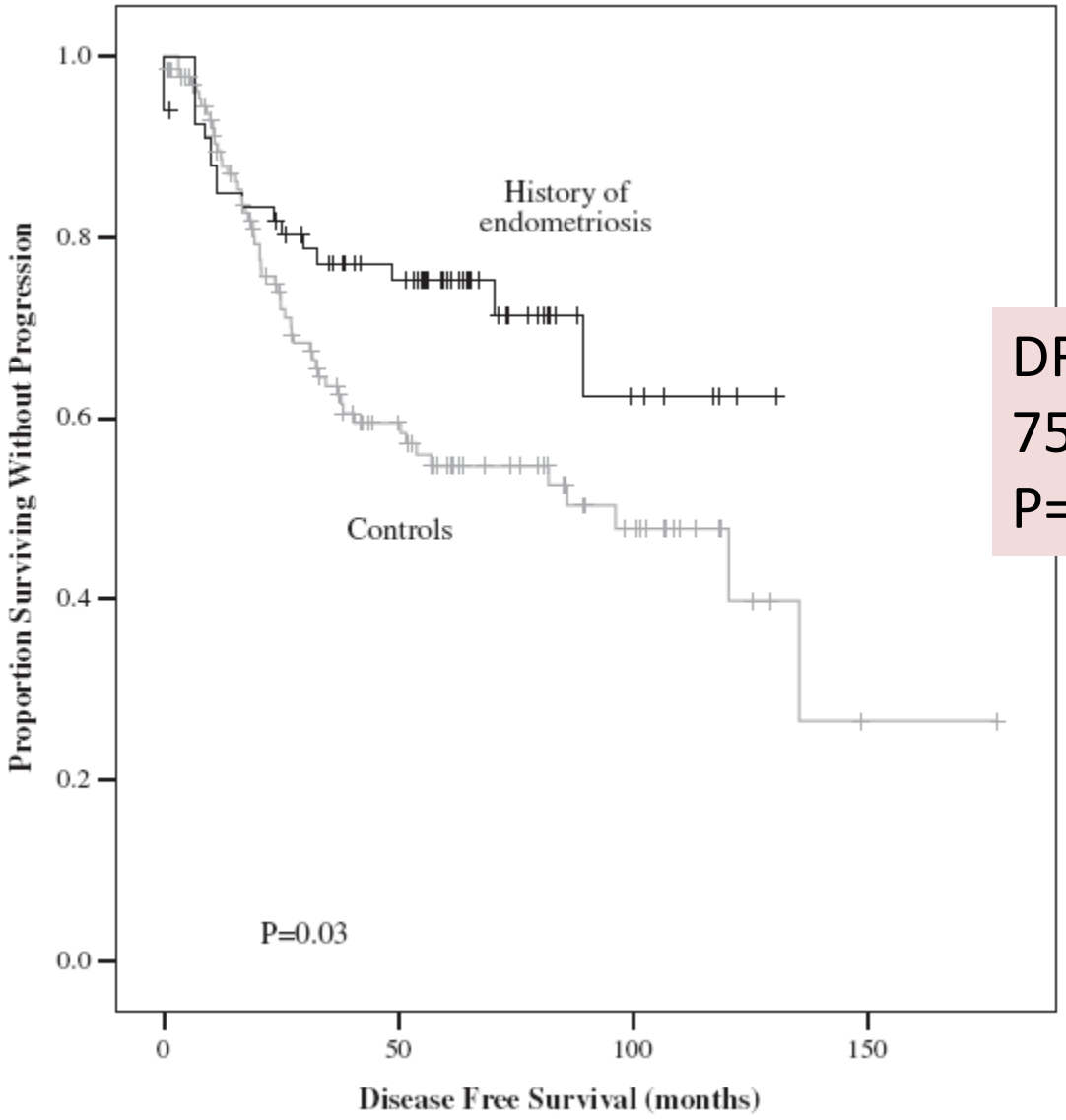
(Peri/postmenop.??)

- ***Atypical/Susp.***
- Size increase (postmen./hormones)
- Mural node(s)
- ≥ 45y
- Symptoms

? *Premalignant # Malignant Endometriosis* ?


EAOCs
• approximately 6y younger
55y vs 62y, p 0.03; Mangili 2012
• 35% more likely to be premenopausal
• earlier Stage at diagnosis
St. I: 88 vs 16%; Wang, 2012
67 vs 28%; Erzen, 2001

5y DFS in EAOCs (N=67) compared with matched PSOC controls (N=134)



DFS
75% vs 55%
P=0.03

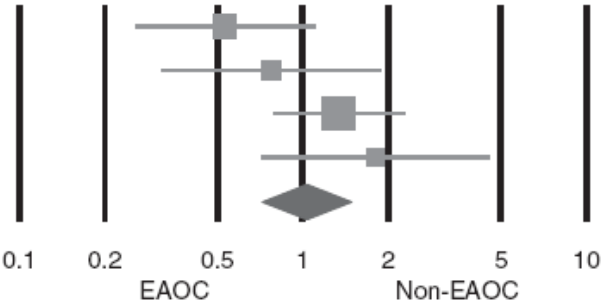
Overall Survival NS

Davis, 2014

Prognosis of EAOC – *Meta-analysis*

PFS
HR 1.023 (0.712-1.470)

8 studies
47.047 pts with EAOC vs non EAOC



OS

	HR	95% CI	*P*
Histology	0.730	0.553–0.964	0.251
FIGO stage			
Early stage (I–II)	0.753	0.494–1.147	0.979
Advanced stage (III–IV)	0.908	0.590–1.397	0.977
Histology			
Clear cell carcinoma	0.820	0.352–1.911	0.098
Adjustment for potential confounding factors			
Age	0.771	0.647–0.918	0.272
Age, grade	0.840	0.578–1.221	0.267
Age, grade, platinum-based chemotherapy	0.966	0.626–1.491	0.303

Kim, 2014

Endometriosis & OC
Open Questions

- Quantify the risk
- Clarify the pathways
- Endometriosis: premalignant lesion
- Type and prognosis of EAOC
- ***Management of (perimenopausal) pts with (history of) endometriomas***

Nat. Cohort Study - *SIR for OC*

Time since E (y)	SIR	(95% CI)
1-4	1.51	1.00-2.18
5-9	**1.78**	**1.30-2.37**
Age at first E (y)		
30-39	1.44	1.10-1.85
>50	**2.27**	**1.61-3.10**

Mogensen, 2016

He et al. Journal of Ovarian Research (2017) 10:45
DOI 10.1186/s13048-017-0343-2

Journal of Ovarian Research

Predictive factors of ovarian carcinoma for women with ovarian endometrioma aged 45 years and older in China

Zheng-Xing He, Hong-Hui Shi, Qing-Bo Fan, Lan Zhu, Jin-Hua Leng*, Da-Wei Sun, Zhan-Fei Li, Keng Shen, Shu Wang* and Jing-He Lang

Institutional study
1038 pts ≥45y
OEM op

Table 3 Multivariate analysis of risk factors of EAOC for OEM patients ≥ 45years[a]

Variable	Category	EAOC		
		OR	95% CI	P
Age	≥50	1.243	0.461–3.348	0.668
	<50			
Postmenopausal status	Yes	3.099	1.050–9.145	0.041*
	No			
Tumor size	≥8 cm	6.566	2.950–14.615	<0.001*
	<8 cm			
Coexisting endometrial disorder	Yes	3.053	1.181–7.889	0.021*
	No			

[a] The multivariate analysis included all patients who had obtained the pathological diagnosis of coexisting endometrial tissue ($n = 693$)

Risk factors of OC in women with E – *Literature Meta-analysis*

Table 4. Risk of ovarian cancer in relation to non-hormonal and other non-surgical investigated risk factors among women with endometriosis.[b]

Author (publication year)	Age	Menopause (yes vs. no)	Parity	Solid complexity vs. not solid	Tumor size
Kadan et al. (2015)[a] (28)	Per 5 year increa			07–138.1)	Per 1 cm increase
Kobayashi et al. (2008) (29)	OR 2.17 (1.29–3 <44 years [c] (reference) ≥45 years[c] HR 8.12 (5.21–1				OR 1.21 (0.99–1.49) <9 cm[c] (reference) ≥9 cm[c] HR 13.5 (8.98–19.3)
Modugno et al. (2005) (24)					
Zanetta et al. (2000) (35)		NS	22 (0.11–0.45) (reference)		

Odds ratio: OR (95% CI), Hazard ratio: HR (95% CI). NS: not significant result (OR, 95% CI and/or p-value not published).

[a]Multivariate analysis.

[b]CA 125: please see text, not in Table.

[c]At endometriosis diagnosis.

E diagnosis >45
Nulliparous
Post-menopausal
Hyperestrogenism
+/- cyst(s) with solid components

Elevated OC Risk

Thomsen, 2017

J Gynecol Oncol. 2018 May;29(3):e28
https://doi.org/10.3802/jgo.2018.29.e28
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Risk factors in progression from endometriosis to ovarian cancer: a cohort study based on medical insurance data

An Jen Chiang,[1,2] Chung Chang,[3] Chi-Hsiang Huang,[3] Wei-Chun Huang,[4,5,6] Yuen-Yee Kan,[7] Jiabin Chen[8,9]

229.617 E pts (2000-13)
1.473 developing OC

Table 3. Independent risk factors in multivariate analysis

Variables	Hazard ratio	p	95% confidence interval
Age (yr)	1.06	<0.001	1.06–1.07
Hospital stratification			
Medical centers	Reference		
Regional hospitals		1	0.57–0.72
District hospitals		1	0.41–0.61
Local hospitals		0	0.09–0.86
Urbanization			
Highly urbanized			
Moderately urbanized		0	0.75–0.96
Newly urbanized		1	0.66–0.91
Rural areas		0	0.65–0.95
Others*		0	0.69–1.10
Premium range (NTD/month)			
>15,840 and ≤25,000			
≤15,840		1	1.10–1.46
>25,000		1	1.10–1.38
Comorbidity			
Depression	1.67	<0.001	1.21–2.30
Pelvic inflammation	2.73	<0.001	2.32–3.22
Childbearing	0.69	0.010	0.52–0.92

Independent factors
Age
Highly urbanized area
Depression
Pelvic inflammation
No post-E childbearing

NTD, New Taiwan Dollar.
*Others includes areas with aged population, agricultural towns and cities, and remote areas.

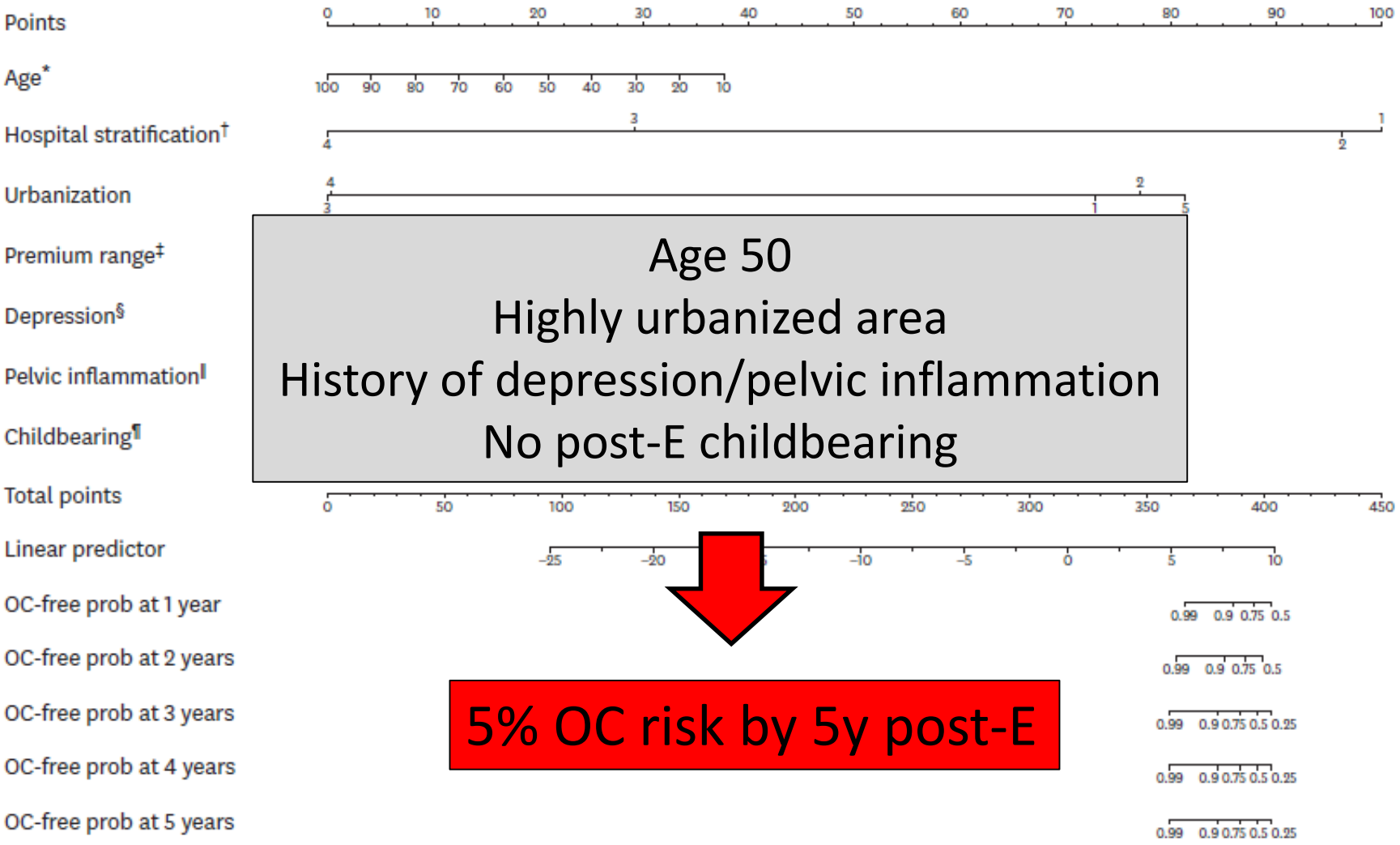


Fig. 1. Nomogram of risk factors in the progression from endometriosis to ovarian cancer.
OC-free prob, ovarian cancer-free probability; NTD, New Taiwan Dollar.
The scales of the risk factors are as follows: *Age: continuous; †Hospital stratification: 1, medical center; 2, regional hospitals; 3, district hospitals; 4, local hospitals; ‡Premium range in NTD: 1, >15,840 and ≤25,000; 2, ≤15,840; 3, >25,000; §Depression: 0, none; 1, history of depression; ‖Pelvic inflammation: 0, none, 1, history of pelvic inflammation; ¶Childbearing: 0, none after endometriosis; 1, history of birth-giving after endometriosis.

Risk of Invasive OC

in relation to diagnosis of Endometriosis, Ovarian Surgery, and by Histotype

Previous Diagnosis of Endometriosis	**Endometrioid/Clear Cell**
	OR
no	1 (ref)
yes	2.8
Ovarian Surgery	
no	**3.2**
yes	1.6
Adnexectomy	**0.8**
Cystectomy/partial res.	3.3

Rossing, 2008

Risk factors of OC in women with E – *Literature Meta-analysis*

Table 5. Risk of ovarian cancer in relation to previous surgical procedures amo g women with endometrios s.

Author (publication year)	Hysterectomy no vs. yes	Sterilization/tubal ligatio No vs. yes	Complete extirpation of endometriosis No vs. yes	Other non-radical procedures
Melin et al. (2013)[a] (26)	OR 1.63 (0.59–4.49)	OR 0.76 (0.30–1.93)[b]	OR 0.29 (0.10–0.84)[a]	OR 0.10 (0.03–0.36)[a] One-sided oophorectomy
Rossing et al. (2008) (10)				OR 0.68 (0.3–1.59) Ovarian surgery after endometriosis diagnosis[c] (yes vs. no)
Melin et al. (2006) (9)	SIR 1.05 (0.63–1.64) vs. SIR 1.54 (1.25–1.86)[d]			
Modugno et al. (2004) (24)	OR 0.69 (0.38–1.24)	OR 0.7 (0.41–1.25)		
Cottreau et al. (2003) (25)	OR 0.6 (0.3–1.2)			
Zanetta et al. (2000) (35)			NS	NS Non-radical extirpation

Odds ratio: OR (95% CI), Hazard ratio: HR (95% CI); NS: not significant result, OR, 95% CI and/or *p*-value not published.

[a]Multivariate analysis.

[b]Only data published including women with adenomyosis.

[c]Includes unilateral oophorectomy, excision of a cyst or part of an ovary.

[d]Hysterectomy at the same time or before a diagnosis of endometriosis had a lower SIR 1.05 (0.63–1.64) than women who did not have this surgical procedure in close relation or before endometriosis diagnosis 1.54 (1.25–1.86).

Thomsen, 2017

Risk factors of OC in women with E – *Literature Meta-analysis*

Table 6. Risk of ovarian cancer in relation to previous hormonal treatment among women with endometriosis.

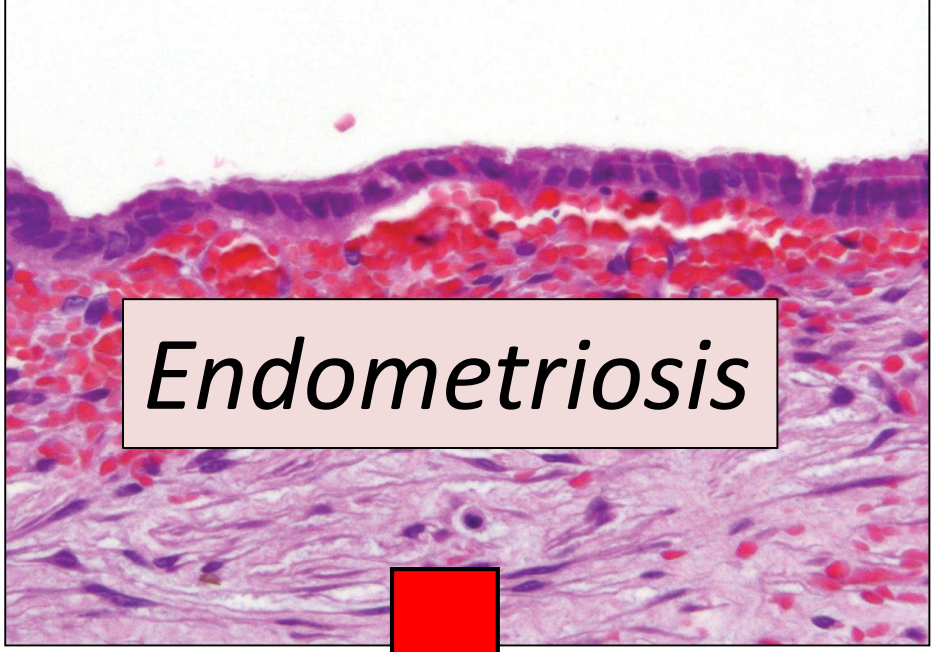
Author (publication year)	Hormone replacement treatment (HRT) with estrogen	BMI	Oral contraceptives	Danazol/Danocrine
Kadan et al. (2015) (28)		NS		
Melin et al. (2013)[a] (26)	Never users (reference) 1–6 months OR 0.65 (0.22–1.86) >6 months OR 2.06 (0.93–4.57)		Never users (reference) 1–12 months OR 0.81 (0.41–1.63)[b] >12 months OR 0.96 (0.44–2.06)[b]	Never users (reference) 1–6 months OR 1.02 (0.44–2.34)[b] >6 months OR 1.32 (0.42–4.13)[b]
Modugno et al. (2004) (24)			Never users (reference) <10 years 0.58 (0.33–1.03) ≥10 years 0.21 (0.08–0.58)	
Cottreau et al. (2003) (25)			Never users (reference) OR 0.5 (0.3–0.9)	Neither medications (reference) OR 2.9 (1.0–8.5)
Zanetta et al. (2000) (35)	NS Unopposed estrogen *or* BMI ≥ 27 $p = 0.05$ OR and 95% CI not published	<27 vs. ≥27 NS	NS	

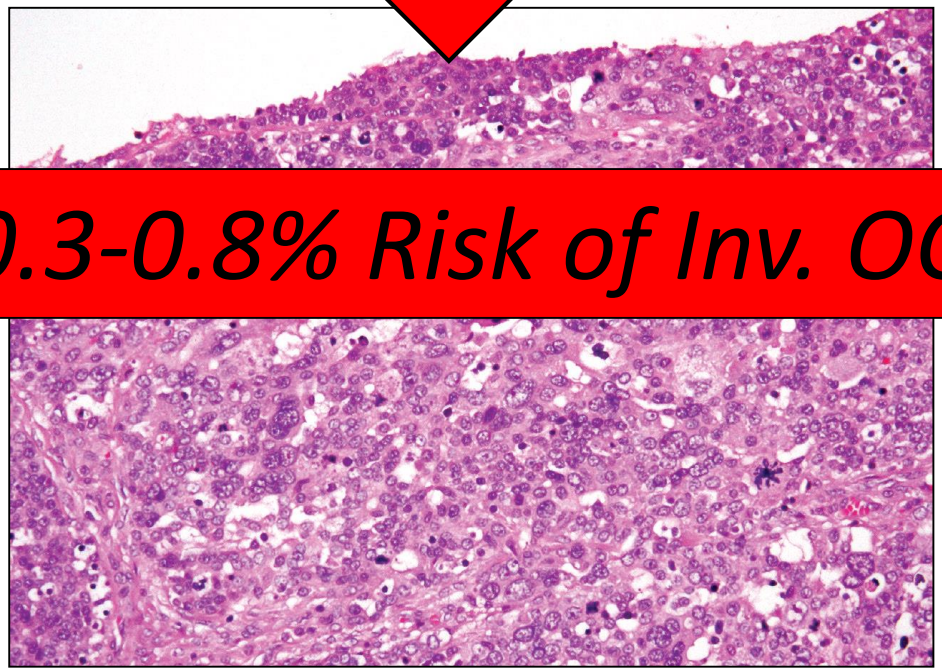
Odds ratio: OR (95% CI), Hazard ratio: HR (95% CI). NS: not significant result, OR, 95% CI and/or p-value not published.

[a]Multivariate analysis.

[b]Including women with adenomyosis.

Thomsen, 2017





0.3-0.8% Risk of Inv. OC

EAOC - Surgery in Perimenopause

women with clinical *typical* endometriosis

Advisable especially in case of
Age ≥45
Nulliparous
OralCs never used

women with only history of endometriosis

Surveillance

Risk-reducing surgery

EAOC - Surveillance in Perimenopause

women with history of endometriosis

No robust data available
in support of systematic screening

EAOC - Risk-red. Surgery in Perimenopause

women with history of endometriosis

No robust data available
in support of systematic surgery

To be discussed with women at high-risk
Familial OC, Infertility, never used OralCs

Endometriosis & OC – *Conclusions. 1*

- E affects up to 10% of women in the reprod. age
- E is associated with a 3-fold increase of ENOC and CCOC
- E: frequent; OC: highly lethal, the link is of scientific high priority and a public health issue
- Models proposed to explain the progression from E to OC, but the full process still to be clarified
- E *per se* not *precancer;* atypical E yes (<5% E cysts removed in premenopause)

Endometriosis & OC – *Conclusions. 2*

- ≥10y OralCs use: significant protection against OC in women with an E history
- In most women with E history only, surveillance rather than RRS advisable
- In women with long-standing typical E, RRS advisable in perimenopause
- Given the (low) progression rate from E to OC, markers should be identified


Multicentre
Italian
Trials
in Ovarian
cancer
MITO