Endometriosis-Associated Ovarian Cancer: Malignant Transformation of Endometriosis

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I have no disclosures.

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Background

- EOC is gynecologic cancer with highest mortality in the US
  - 22,240 women dx and 14,030 deaths in 2013
- 70% of cases have serous histology
- Clear cell accounts for 12% and second-leading mortality cause from EOC
  - Genetically stable
  - Low mitotic rate
  - Lacks chromosomal instability

ACS. Facts & Figures, 2013.
Sugiyam et al. Cancer 2000;88:2584-9
Crotzer et al. Gynecol Oncol 2007;105:404-8

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Background

- Endometriosis considered benign, chronic gynecologic disorder
- Exact prevalence not known since many are symptomatic and definitive dx made histologically
- Estimates
  - 10% of premenopausal women
  - 4% of postmenopausal women
  - 35-40% of women with infertility or chronic pelvic pain

Olive et al. N Engl J Med 1993;328:1759-69
Giudice et al. Lancet 2004;364:1789-66
Punnonen et al. Eur J Obstet Gynecol Reprod Biol 1980;11:195-200

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Background

- Noteworthy association between endometriosis and clear cell, endometriod EOC
  - Cohort study in Denmark (1978-1998)
  - Increased risk of EOC in women with endometriosis restricted to 2 histologies
    - Endometrioid (RR, 2.53; 95%CI 1.19-5.38)
    - Clear cell (RR, 3.37; 95% CI 1.24-9.14)

Brinton et al. Cancer Epidemiol Biomar Prev 2005;14:2929-35

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Background

- Controversy over causality of relationship
  - Invasive cancer may obliterate endometriosis
  - Endometriotic implants may be missed on histologic examination
  - Difficult to distinguish b/w endometriosis not related to cancer and endometriosis that may have undergone malignant transformation

Nishida et al. Gynecol Obstet Invest 2000;50:18-25
Steed et al. J Obstet Gynaecol Can 2004;26:709-15
Nezhat et al. Fertil Steril 2008;90:1559-70

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Background

- Endometriosis shares common features with malignancies
  - Can attach and adhere to other tissue
  - Can invade locally and metastasize distantly
- Endometriosis unlike cancer does not have catabolic potential and is almost never fatal

Munksgaard et al. Gynecol Oncol 2011:123:157-63
Vlahos et al. Best Pract Res Clin Obstet Gynaecol 2011;24:39-50

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Relationship Between Endometriosis and EOC: Sampson's Criteria

- Endometriosis must be present in close proximity to tumor
- No other primary site for tumor identified
- Tissue resembling endometrial stroma surrounding glands must be present
- Scott's additional requirement
  - Histologically proven transition from endometriosis to cancer

Sampson JA. Ann Surg 1925:10:1-12
Scott R. Obstet Gynecol 1953;2:283-89

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Epidemiology

- Data from large cohort and case-control studies indicate association between endometriosis and increased risk of EOC is modest
- Cohort studies and case-control studies
  - Swedish National Board of Health and Welfare
  - National Swedish Cancer Registry
  - Shizouka Cancer Registry

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Cohort Studies Evaluating Cancer Risk in Patients with Endometriosis

Author	# of Patients	F/U Time (Years)	Overall Cancer Risk		EOC Cancer Risk	
			SIR	95% CI	SIR	95% CI
Brinton	20,686	11.4	1.2	1.1-1.3	1.9	1.3-2.8
Melin	64,492	12.7	1.0	0.9-1.1	1.4	1.2-1.7
Melin	63,630	13.4			1.37	1.14-1.62
Kobayahsi	6,398	12.8	8.95	4.12-5.3	13.2	6.9-20.9
Brinton	12,193	18.8			2.48	1.3-4.2
Olsen	1,392	13			0.78 (RR)	0.25-2.44

EOC=epithelial ovarian cancer; SIR=standardized incidence ratio; CI=confidence interval; RR=relative risk

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Case-Control Studies Evaluating EOC Risk in Patients with Endometriosis

Author	# of Cases	# of Controls	EOC Cancer Risk	
			RR	95% CI
Ness	767	1,367	1.7	1.2-2.4
Ness	5,207	7,705	1.73	1.10-2.71
Modugno	2,098	2,953	1.32	1.06-1.65
Borgfeldt	28,163	3 controls per case	1.34	1.03-1.65
Rossing	812	1,313	1.5	1.1-2.1
Brinton	104,561	99,812	1.69	1.27-2.25

EOC=epithelial ovarian cancer; RR=relative risk; CI=confidence interval

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Association between history of endometriosis and the histological subtypes of ovarian cancer (Pearce et al., 2012)

	Crude		Stratified only		Stratified and adjusted	
	OR (95% CI)	p value	OR (95% CI)*	p value	OR (95% CI)	p value
Invasive	1·49 (1·34–1·65)	<0·0001	1·53 (1·37–1·70)	<0·0001	1·46 (1·31–1·63)	<0·0001
Clear-cell	3·73 (3·04–4·58)	<0·0001	3·44 (2·78–4·27)	<0·0001	3·05 (2·43–3·84)	<0·0001
Endometrioid	2·32 (1·94–2·78)	<0·0001	2·20 (1·82–2·66)	<0·0001	2·04 (1·67–2·48)	<0·0001
Mucinous	1·09 (0·76–1·58)	0·63	1·04 (0·71–1·51)	0·86	1·02 (0·69–1·50)	0·93
High-grade serous	1·11 (0·96–1·29)	0·16	1·16 (1·00–1·35)	0·056	1·13 (0·97–1·32)	0·13
Low-grade serous	2·02 (1·38–2·97)	<0·0001	2·22 (1·48–3·31)	<0·0001	2·11 (1·39–3·20)	<0·0001
Borderline	1·26 (1·05–1·50)	0·012	1·19 (0·99–1·43)	0·062	1·12 (0·93–1·35)	0·24
Mucinous	1·27 (0·97–1·67)	0·078	1·19 (0·90–1·57)	0·23	1·12 (0·84–1·48)	0·45
Serous	1·31 (1·05–1·63)	0·015	1·28 (1·02–1·61)	0·034	1·20 (0·95–1·52)	0·12

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Pathology

- Common genetic alterations in allelotyping of endometriosis along with adjacent EOC
- Genetic defects only in carcinoma and not in benign epithelium

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Atypical Endometriosis: Precursor to Cancer

- Cytologic atypia and hyperplasia documented in endometriosis
- May represent transition from endometriosis to cancer
- 194 cases of ovarian endometriosis[1]
  - Cytologic atypia (severe, 3.6%; mild 22%)
  - Hyperplasia 2%
- [2]Severe atypia in 14 (100%) EAOC and 6 (2%) controls
- [3]Atypical endometriosis in 61% of EAOC and 1.7% of controls
- [4]Severe atypia in 29/37 (78%) EAOC cases, transition from typical to atypical endometriosis in 22 cases and transition from atypical endometriosis to cancer in 23 cases

[1]Czernobilsky, et al. Obstet Gynecol 1979;53:318-23
[2]Perfumo et al. Gynecol Oncol 2002;84:280-84
[3]Fukanga et al. Histopathology 1997;30:249-55.
[4]Ogawa et al. Gynecol Oncol 2000;77:298-304

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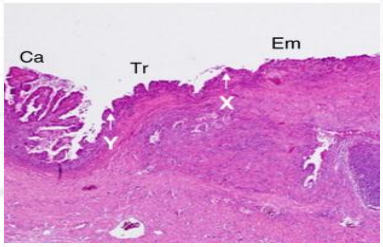
Atypical Endometriosis



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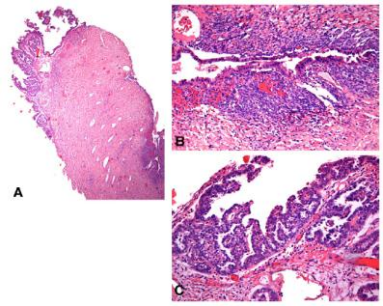

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Hyperplasia as Precursor to Cancer

- CH seen in association with cytologic atypia
- Role as independent precursor in EAOC remains elusive
- Complex hyperplasia
  - 50% of 14 EAOC cases
  - 1% of 325 controls ($p<0.0001$)

Perfumo et al. Gynecol Oncol 2002;84:280-84

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Pathogenesis: Genetic Alterations

- Genomic instability and clonal outgrowth are fundamental in oncogenesis
- Loss of heterozygosity (LOH)
  - [1]LOH at ovarian suppressor gene loci seen in 11/40 (27.5%) of endometriosis samples
  - [2]Common LOH event in 9/11 cases of ovarian endometriosis adjacent to ovarian carcinoma
  - [3]LOH events accumulate as disease progresses

[1]Jiang et al. Cancer Res 1996;56:3534-9
[2]Jiang et al. Cancer Res 1998;58:1707-12
[3]Munksgaard et al. Gynecol Oncol 2012;124:164-69

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PTEN

PTEN inactivation may be early event in malignant transformation of endometriosis

Mutations occur in both endometrial and ovarian carcinomas

Histology	Inactivation (LOH)	Somatic PTEN Mutation
Endometriotic Ovarian Cyst	13/23 (56.6%)	5/23 (20.6%)
Endometrioid EOC	8/19 (42.1%)	4/19 (20%)
Clear Cell EOC	6/22 (27.3%)	2/22 (8.3%)

Sato et al. Cancer Res 2000;60:7052-6

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PTEN

Mouse model of endometriosis and endometrioid ovarian cancer

- KRAS over-expression
- PTEN knockout in ovarian surface epithelium

Resulted in endometrial morphology

Suggests potential role these genetic changes may play in malignant transformation

Dinulescu et al. Nat Med 2005;11:63-70

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p53

- Mutation or loss of function critical even in development of EOC
- Not seen in endometriosis that is not associated with carcinoma
- Chromosomal loss of p53 in severe endometriosis
  - (Biscoff et al., 2002)
- p53 accumulation within endometriosis that is adjacent to carcinoma compared to endometriosis without carcinoma
  - (Nezhat et al., 2002)
- Several other series have not been able to reproduce these results

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ARID1A

- AT-rich interactive domain 1A gene
- Tumor suppressor gene
- Encodes for BAF250a protein
  - Plays critical role in SWI-SNF complex present in all eukaryotes
  - Responsible for regulating critical cellular processes and gene expression

Wiegand et al. N Engl J Med 201363:1532-430

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ARID1A

Results

- 6 of 18 samples had somatic mutations in *ARID1A*
- *ARID1A* mutations were found in
  - 55 of 119 (46%) ovarian clear cell carcinomas
  - 10 of 33 (30%) endometrioid carcinomas
  - None of 76 high-grade serous carcinomas
- IHC analysis confirmed loss of expression of BAF250 protein that correlated with ARID1A mutational status
- In 2 cases, endometriotic lesions adjacent to the tumor had the same mutations as were found in the cancer

Wiegand et al. N Engl J Med 201363:1532-430

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ARID1A

- 2 sets of patient samples of EAOC (clear cell) with contiguous atypical endometriosis evaluated
  - ARID1A mutations seen in primary malignant lesion
  - ARID1A mutations seen in contiguous atypical endometriosis
  - ARID1A expression retained in areas of endometriosis distant from primary malignant lesion

Wiegand et al. N Engl J Med 201363:1532-430

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ARID1A

- Mutations have also been found in low-grade uterine carcinomas
- Treatment strategy?
  - Loss of ARID1A activates transcriptional events that may be targetable
- Prevention strategy?
  - BAF250a expression in endometriotic lesions to identify lesions at risk of malignant transformation

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Estrogen

- Aromatase
  - Catalyzes conversion of androstenedione and testosterone from ovary and adrenals to estrone and estradiol (E2)
  - Absent in endometrium
  - High concentrations in endometriotic lesions
    - Increased conversion of androgens to estrogens
- 17-β-hydroxysteroid dehydrogenase type 2
  - Converts more potent E2 to less potent estrone
  - Present in eutopic endometrium
  - Absent in endometriotic lesions
- Result is increased levels of E2 by increased production and decreased inactivation

Munksgaard et al. Gynecol Oncol 2012;125:164-69
Zeitun et al. J Clin Endocrinol Metab 1998;83:4474-80

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Endometriosis-Associated Ovarian Cancer: A Distinct Clinical Entity?

- Younger
- Diagnosed at earlier stage
- Lower grade lesions
- Better prognosis
  (even when adjusting for stage)

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EAOC: An Entity Distinct from Other Ovarian Carcinomas

- 58 patients with EAOC nested with four age-matched non-EAOC controls
- Patients with EAOC proved to:
  - Lower stage ($p<0.001$)
  - Over-expression of clear cell and endometrioid histologies ($p=0.0001$)
  - Lower grade lesions ($p=0.03$)
  - Optimally debulked to no gross residual disease ($p=0.0001$)
  - Significantly better OS ($p=0.0001$)

Erzen et al. Gynecol Oncol 2001;83:100-8

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Endometrioid Ovarian Cancer

Retrospective review of patients with endometrioid ovarian cancer
Sampson's/Scott's criteria to define association with endometriosis
21 patients with EAEOC vs. 44 patients with EOC
EAEOC patients were

- Younger
- Lower stage of disease
- Higher prevalence of low grade tumors
- More concomitant endometrial cancers (with 92% concordance in grade)
- No significant difference in survival (5-yr survival 44% vs. 38%, p=0.47)
- Age was the only significant predictor of survival

Mangili et al. Gynecol Oncol 2012;126:403-7

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Retrospective Analysis of Presentation, Treatment, and Outcome

Objective
- To investigate the relationship of menopausal status and tumors arising in endometriosis

Behavior and outcome of different histologies of epithelial ovarian cancer known to arise from endometriosis were analyzed

Garrett et al. J Reprod Med, 2013;58 (6):469-76

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Results

- 140 patients with complete clinical information
  - 42 (30%) clear cell carcinoma
  - 92 (65.7%) endometrioid carcinoma
  - 6 (4.3%) mixed serous, clear cell, and endometrioid carcinoma
- Relationship with endometriosis
  - 28.6% were "associated with" endometriosis (n=40)
  - 37.1% were "arising in" endometriosis (n=52)
  - 34.3% had no endometriosis (n=48)

Garrett et al. J Reprod Med, 2013; 158 (6):469-76

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Clear Cell Carcinoma (n=42)

	Premenopausal N (%)	Postmenopausal N (%)	p-value, chi square
Total	13 (31.0%)	29 (69.0%)	
Average Age at Dx	41.4 ± 6.1	57.2 ± 8.1	p<.001*
Stage 1-2	11 (84.6%)	14 (48.3%)	p=0.03
Stage 3-4	2 (15.4%)	15 (51.7%)	
Grade 1-2	2 (15.4%)	5 (17.2%)	p=0.88
Grade 3	11 (84.6%)	24 (82.8%)	
Arising in Endometriosis	6 (46.2%)	7 (24.1%)	p=0.05
Associated with Endometriosis	6 (46.2%)	12 (41.4%)	p=0.14
No endometriosis	1 (7.7%)	10 (34.5%)	p=0.07

*Univariate analysis with Student's T test

Garrett et al. J Reprod Med, 2013; 58 (6):469-76

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Endometrioid Carcinoma (n=92)

	Premenopausal N (%)	Postmenopausal N (%)	p-value, chi square
Total	30 (32.6%)	62 (67.4%)	
Average Age at Diagnosis	42.2 ± 4.4	59.7 ± 7.4	p<.001
Stage 1-2	23 (76.7%)	48 (77.4%)	p=0.94
Stage 3-4	7 (23.3%)	14 (22.6%)	
Grade 1-2	25 (83.3%)	43 (69.4%)	p=0.15
Grade 3	5 (16.7%)	19 (30.6%)	
Arising in Endometriosis	19 (63.3%)	19 (30.6%)	p<0.01
Associated with Endometriosis	4 (13.3%)	14 (22.6%)	p=0.81
No endometriosis	7 (23.3%)	29 (46.8%)	p=0.03

Garrett et al. J Reprod Med, 2013; 58 (6):469-76

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Recurrences & Deaths by Menopausal Status

	Pre-menopausal	Postmenopausal	p-value
Clear Cell			
Median F/U (months)	41 (1-93)	30 (1-105)	p=0.56
Recurrences	1 (7.7%)	13 (44.8%)	p< 0.02
Death	1 (7.7%)	13 (44.8%)	p< 0.02
Endometrioid			
Median F/U (months)	51.5 (4-95)	36 (1-109)	p=0.05
Recurrences	6 (20.0%)	14 (22.6%)	p=0.78
Death	3 (10.0%)	9 (14.5%)	p=0.55

Garrett et al. J Reprod Med, 2013; 58 (6):469-76

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Recurrences & Deaths by Relationship with Endometriosis

	Arising in Endometriosis	No Endometriosis	p-value
Clear Cell			
Median F/U (months)	29 (1-66)	48 (1-98)	p=0.46
Recurrences	4 (30.8%)	5 (45.4%)	p=0.46
Death	3 (23.1%)	5 (45.4%)	p=0.25
Endometrioid			
Median F/U (months)	48 (10-109)	39 (1-98)	p=0.56
Recurrences	5 (13.2%)	12 (33.3%)	p=0.04
Death	3 (7.9%)	7 (19.4%)	p=0.15

Garrett et al. J Reprod Med, 2013; 58 (6):469-76

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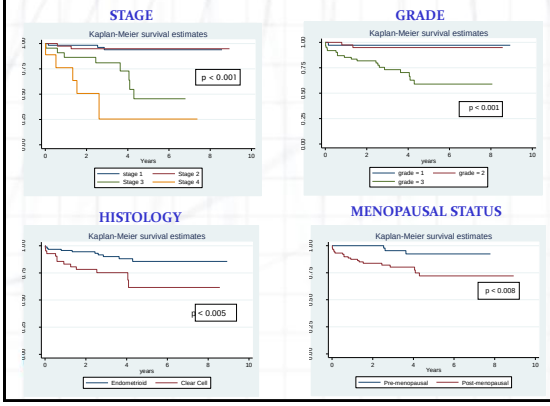
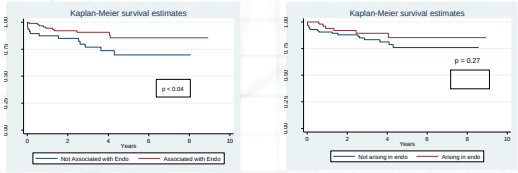


Survival and Endometriosis



The association of endometriosis with improved survival was slightly attenuated and no longer statistically significant after adjustment for menopausal status (p=0.07)

Garrett et al. J Reprod Med, 2013; 58 (6):469-76

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Case Control Study: EAOC-Serous EOC

- 67 cases and 134 controls
  - 41 with endometrioid EAOC
  - 26 with clear cell EAOC
- Matched by age, date of dx, stage

Davis et al. Gynecol Oncol 2014 (In Press)

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Case Control Study: EAOC-Serous EOC

- Stage I: 27 (40.3%)
- Stage II: 27 (40.3%)
- Stage III: 10 (14.9%)
- Stage IV: 3 (4.5%)
- No difference between groups with respect to
  - CA-125 level at dx
  - Rate of optimal cytoreduction
  - Tx with platinum-based therapy
- 69.6% of patients with EAOC had synchronous EC vs 13.5% of controls (p<0.001)

Davis et al. Gynecol Oncol 2014 (In Press)

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Results

Variable	EAOC (n=67)	Control (n =134)	p value
Mean Age	51.7	56.6	0.005*
Mean CA-125	268.8	377.1	.341
Stage:			
I	27	54	
II	27	52	
III	10	22	
IV	3	6	0.998
Cytoreduction:			
Optimal < 1cm	65	116	
Suboptimal	2	18	0.458
Chemotherapy:			
Platinum	39	81	0.521
Taxol	38	73	0.614
Both	39	73	0.391

Difference within +/- 5 yrs of age at time of Dx

Davis et al. Gynecol Oncol 2014 (In Press)

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Results

Other Cancers	EAOC (n =67)	Control (n =134)	p value
Recurrence	20	55	0.03
Deaths	7	15	0.596
Survival	40	64	0.280
Response to chemotherapy:			
CR	62	73	
PR	4	13	
PD	1	48	0.343
Platinum Resistant	6	7	0.199
XRT	6	4	0.057

Davis et al. Gynecol Oncol 2014 (In Press)

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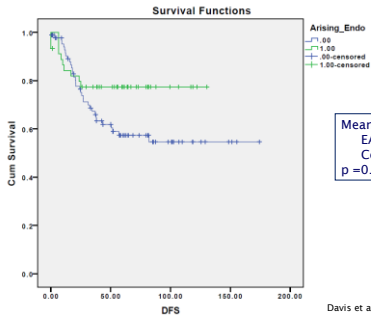
5-Year DFI



Mean DFS (months)
EAOC= 103.2
Control = 71
p =0.03

Davis et al. Gynecol Oncol 2014 (In Press)

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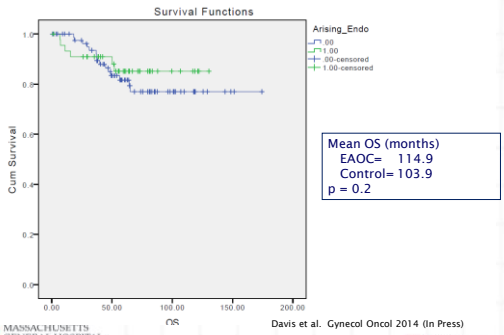
OS Survival



Mean OS (months)
EAOC= 114.9
Control= 103.9
p = 0.2

Davis et al. Gynecol Oncol 2014 (In Press)

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Conclusions

- Patients with EAOC had higher rate of synchronous EC
- No difference in demographic or tx patterns between cases and controls
- Lower rate of recurrence and improved 5-year DFI in EAOC
- No OS difference between cases and controls

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Conclusions

- Association between endometriosis and EOC supported by epidemiologic research
- Molecular pathway poorly defined
- Micro-environment of endometriosis and EAOC share cytokines and mediators
  - ? Link or sharing of common signaling molecules of 2 separate lesions
- Future studies to elucidate roles of oxidative stress, inflammation and estrogen in development of EAOC
  - Impact patient counseling
  - Clinically relevant interventions, risk reduction

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Future Directions

- Identification of endometriotic lesions at greatest risk of malignant transformation
- Better understanding may lead to preventative strategies for those at greatest risk of EAOC and development of novel therapies

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Thank You

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