Epidemiology of endometriosis: is there an association with cancer?

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Endometriosis and Ovarian Cancer

Endometriosis is believed to be a precursor lesion for ovarian cancer.

Laparoscopy:
Ovarian Endometrioma

Endometriosis – Similarities to Cancer

Invasion of surrounding organs

Bowel
Endometriosis

Endometriosis – Similarities to Cancer

Damage of neighboring tissues

Ureter obstruction
by deep infiltrating
endometriosis implant

Similarities of Endometriosis and Cancer: 2 Hypotheses

1. Endometriotic implants may directly undergo malignant transformation, perhaps through an atypical transition phase

Varma et al. 2004; Reprod Review 127: 293 – 304
Endometriosis and the neoplastic process

Our data:
L1CAM – Cell Adhesion Molecule

- L1CAM is a transmembrane glycoprotein (200-240 kD)
- L1CAM regulates and promotes the cell migration and adhesion
- High concentrations of L1CAM are described in different types of cancer (f. e. ovarian cancer)

Transition from Endometriosis to Atypical Endometriosis L1CAM – Cell Adhesion Molecule

- Normal endometrium
- Typical ovarian endometriosis: 11,8 % L1 positive (2/17)
- Atypical ovarian endometriosis 92,9 % L1 positive (13/14)

Finas et al. 2008, Hum Reprod; 23:1053-1062.
L1 cell adhesion molecule (L1CAM) as a pathogenic factor in endometriosis

Similarities of Endometriosis and Cancer: 2 Hypotheses

2. Endometriosis and cancer share common antecedent mechanisms and/or predisposing factors (genetic susceptibility, immune/ angiogenic dysregulation, environmental toxin exposure).

Varma et al. 2004; Reprod Review 127: 293 – 304
Endometriosis and the neoplastic process

The Hallmarks of Cancer

1. Self-sufficiency in growth signals
2. Insensivity to anti-proliferative signals
3. Resistance to apoptosis – Limitless replicative potential
4. Sustained angiogenesis
5. Tissue invasion and metastasis
6. Genomic instability

Varma et al. 2004; Reprod Review 127: 293 – 304
Endometriosis and the neoplastic process

Endometriosis and Cancer Risk

For patients with endometriosis, the overall risk of cancer is estimated to be around 0.7 to 1.0%, suggesting, that endometriosis is not associated with an increased risk of cancer in general.

Heaps et al., Obstet Gynecol 1990; 75: 1023-28.
Malignant neoplasms arising in endometriosis.

Endometriosis and Cancer Risk

An increased risk of some types of malignancy has been shown for patients with endometriosis:

ovarian cancer (endometrioid, clear-cell)	SIR 1.43
non-Hodgkin-lymphoma	SIR 1.24
endocrine tumors	SIR 1.36
brain tumors	SIR 1.22.

Endometriosis – Higher Prevalence for Ovarian Cancer

Retrospective observational cohort study (12,193 patients):

Endometriosis – Ovarian Cancer:

Standardized Incidence Ratio (SIR) 2.48

Endometriosis + primary infertility – Ovarian Cancer:

Standardized Incidence Ratio (SIR) 4.2

Brinton et al., Fertil Steril 2004; 82: 405-414
Ovarian cancer risk associated with varying causes of infertility

Endometriosis – Higher Prevalence for Ovarian Cancer

Another population-based case-control study:

Endometriosis – Ovarian Cancer:

Standardized Incidence Ratio (SIR) 1.7

Ness et al., 2000. Epidemiology 11.2 : 111-17.
Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer.

Endometrioid and Clear Cell Ovarian Cancers – Risk Factors

Decreased risk:
- Increasing parity
- OC for => 5 years
- breast feeding
- tubal ligation

Increased risk:
- endometriosis OR 2.2 endometrioid
  OR 3.0 clear cell

Nagle et al., 2008. Eur J Cancer; 44: 2477-2484
Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors

Endometriosis and Cancer Risk

- For cervical cancer, the SIR is decreased (SIR 0.7)
- The risk for uterine cancer (SIR 1.1) is not changed
- Adenomyosis is not related to an increased cancer risk.

Brinton et al., 2005 Cancer Epidemiol Biomarkers Prev ; 14.12 : 2929-2935. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors

Olson et al. 2002; Cancer 94.5: 1612-18
Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study

Endometriosis – Higher Prevalence for Ovarian Cancer

Review of an ovarian endometrioma cohort (6398)
follow up of 17 years: 46 ovarian cancers

Standardized Incidence Ratio (SIR) 8.95

Independent predictors: age > 40 years
endometrioma size > 9 cm
slightly elevated CA-125

Kobayashi 2009, Int J Clin Oncol; 14: 378-382
Ovarian cancer in endometriosis: epidemiology, natural history, and clinical diagnosis

Endometriosis and Cancer Risk

Critical evaluation of observational, cohort, and case-control studies performed in order to assess the association between endometriosis and malignant diseases, did not confirm the increased risk of malignancy in endometriosis in general.

Evidence for an association with melanoma and non-Hodgkin's lymphoma is suggested whereas an increased risk for other gynecological cancer types is not supported.

Somigliana et al, 2006 Gynecol Oncol 101.2 : 331-41
Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence.

Association between Endometrioid Ovarian Carcinoma and Endometriosis

9 – 70% of endometrioid ovarian carcinoma or clear cell carcinoma are associated with endometriosis

Stern et al., Int J Gynecol Pathol 2001; 20: 133-139
Malignancy in endometriosis: frequency and comparison of ovarian and extraovarian types.

Erzen et al., Gynecol Oncol 2001; 83: 100-108
Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct from other ovarian carcinomas as suggested by a nested case-control study

Modesitt et al., Obstet Gynecol 2002; 100: 788-795
Ovarian and extraovarian endometriosis-associated cancer

Somigliana et al, 2006 Gynecol Oncol 101.2 : 331-41
Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence

EAOC compared to Ovarian Carcinoma

EAOC, compared with other ovarian cancers without endometriosis, presents :

- at a less-advanced stage
- lower grade
- predominantly endometrioid and clear-cell type
- with a better overall survival

Van Gorp et al. 2004
Leiserowitz et al. 2003
Modesitt et al. 2002
Erzen et al. 2001
Komiyama et al. 1999

Loss of Heterozygosity

Loss of heterozygosity of the same allels in co-existing ovarian carcinoma and endometriosis samples.

Examination of 10 EAOCs (4 endometrioid, 6 clear cell)

63 LOH in carcinoma samples

22 LOH also in endometriosis samples (same allel lost)

No LOH in endometriosis alone

Prowse et al., Int J Cancer 2006; 119: 556-562
Molecular genetic evidence that endometriosis is a precursor of ovarian cancer.

Loss of Heterozygosity

Loss of heterozygosity on 10q23.3:

ovarian endometrioid carcinomas	41% LOH (8/19)
clear cell carcinomas	27% LOH (6/22)
solitary endometrioid cysts	56% LOH (13/23)

Sato et al., Cancer Res 2000; 60: 7052 - 7056
Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinomy of the ovary

Mutation of PTEN

Mutation of the tumor suppressor gene PTEN:

ovarian endometrioid carcinomas	20% (4/20)
clear cell carcinomas	8% (2/24)
solitary endometrioid cysts	21% (7/34)

Sato et al., Cancer Res 2000; 60: 7052 - 7056
Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinomy of the ovary

Mutation of K-ras and PTEN

In mice with an oncogenic allele of *K-ras* resulting in the development of benign lesions reminiscent of endometriosis, a conditional deletion of *PTEN* caused the progression toward ovarian cancer. They were diagnosed as endometrioid subtype.

Any evidence of a similar phenomenon in humans is presently lacking.

Dinulescu et al., 2005 Nat Med 11.1: 63-70
Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer

Molecular pathogenesis of EAOC

Transportation of highly pro-oxidant factors like heme and iron into the peritoneal cavity or ovarian endometrioma.

Genetic damages caused by iron-dependent oxidative stress.

DNA damage or LOH by oxidative stress.

Kobayashi et al., 2009 Oncol Rep; 22: 233-240
Molecular pathogenesis of endometriosis-associated clear cell carcinoma of the ovary (review)

Molecular pathogenesis of EAOC

LOH studies found involvement of specific chromosomal regions:

5q, 6q, 9p, 10q, 11q, 17q, 22q

Genes involved in CCC carcinogenesis:

PTEN, APC, p53, polo-like kinase, Emi1, K-ras

Kobayashi et al., 2009 Oncol Rep; 22: 233-240
Molecular pathogenesis of endometriosis-associated clear cell carcinoma of the ovary (review)

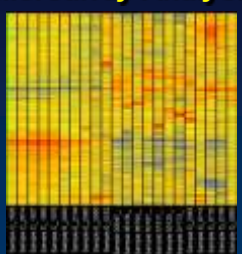
Our Data: Microarray Analysis

Affymetrix-Chip HG-U133A, data analysis by Microarray Suite Version 5.0, 22.283 Genes examined:

5 endometriosis:	age 36.4 ± 7.4 years; all premenopausal
7 EAOC:	age 58.8 ± 13.2 years; 1 premenopausal, 6 postmenopausal
5 OC:	age 57.8 ± 13.0 years; 2 premenopausal, 3 postmenopausal
5 benign ovaries:	age 48.3 ± 22.7 years; 2 premenopausal, 3 postmenopausal

Banz et al., Fertil Steril 2009; 60: 7052 - 7056
The Molecular Signature of Endometrioid Ovarian Cancer Associated with Endometriosis (EAOC) Differs Significantly from Endometrioid Ovarian Cancer which is Endometriosis Independent (OC)

Microarray Analysis



benign N = 5 | Endom. N = 5 | EAOC N = 7 | OC N = 5

Quantitative real time PCR

14 endometriosis:	age 34.8 ± 6.3 years; all premenopausal
8 EAOC:	age 58.5 ± 12.6 years; 1 premenopausal, 7 postmenopausal
16 OC:	age 65.6 ± 12.1 years; 2 premenopausal, 14 postmenopausal
9 benign ovaries:	age 50.8 ± 16.3 years; 4 premenopausal, 5 postmenopausal

Banz et al., Fertil Steril 2009; 60: 7052 - 7056
The Molecular Signature of Endometrioid Ovarian Cancer Associated with Endometriosis (EAOC) Differs Significantly from Endometrioid Ovarian Cancer which is Endometriosis Independent (OC)

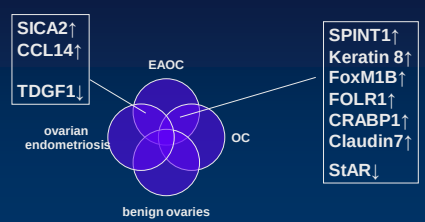
Differentially expressed Genes were listed in two Main Groups:

1) Genes up- or down-regulated in endometriosis and EAOC versus OC and benign ovaries

2) Genes that are up- or downregulated in EAOC and OC versus ovarian endometriosis and benign ovaries

Banz et al., Fertil Steril 2009; 60: 7052 - 7056
The Molecular Signature of Endometrioid Ovarian Cancer Associated with Endometriosis (EAOC) Differs Significantly from Endometrioid Ovarian Cancer which is Endometriosis Independent (OC)

Diagram of Genes equally up- or downregulated in EAOC and OC or EAOC and Ovarian Endometriosis



Genes equally expresses in EAOC and Ovarian Endometriosis versus OC and Benign Ovaries

Upregulated:	CCL14, small inducible cytokine subfamily A, member 14 SICA2, small inducible cytokine A2 (= MCP1)
Downregulated:	TDGF1, Teratocarcinoma-derived growth factor 1

Up-regulated in EAOC and Endometriosis CCL 14 and SICA 2 (MCP-1)

- Members of the small inducible gene family (SIG)
- Recruitment of monocytes to sites of injury and infection
- Secreted by endothelial cells, fibroblasts and leukocytes
- Chemokines affect tumor development by attracting immunocompetent cells with pro- and anti-tumoral activities

Down-regulated in EAOC and Endometriosis: Teratocarcinoma-derived growth factor (TDGF, Cripto-1):

- Similarity to human transforming growth factor alpha and epidermal growth factor
- Role of TDGF for embryogenesis, cell migration, invasion and angiogenesis
- TDGF is expressed in 47% of ovarian cancer samples

Genes equally expressed in EAOC and OC versus Ovarian Endometriosis and Benign Ovaries

Upregulated:	SPINT1, Serine protease inhibitor, type 1 Keratin 8 FoxM1B, forkhead box M1 FOLR1, Folate receptor 1 CRABP1, cellular retinoic acid binding protein 1 Claudin7
Downregulated:	StAR, Steroidogenic acute regulatory protein

Genes up-regulated in EAOC and OC: Serin protease inhibitor 1 (SPINT1)

SPINT-1 inhibits biological active Hepatocyte Growth Factor (HGF), which stimulates:

- tumor cell-cell-interaction
- matrix adhesions
- migration
- angiogenesis

Genes up-regulated in EAOC and OC: Keratin-8

Keratin-8:

- Intermediary filament
- Involved in cell motility and cancer progression

Genes up-regulated in EAOC and OC: Forkhead Box M1B transcription factor (FoxM1B)

FoxM1B:

- Trancription factor
- Regulates expression of cell cycle genes essential for progression into DNA replication and mitosis

Genes up-regulated in EAOC and OC: Folate Receptor 1 (FOLR1)

FOLR1:

- High affinity for folic acid and folic acid derivates
- Mediates delivery of 5-methyl-tetrahydrofolate to the interior of cells
- Marker for ovarian cancer

Genes up-regulated in EAOC and OC: Retinoic acid-binding protein type 1 (CRABP1)

CRABP1:

- Important role in retinoic-acid-mediated differentiation and proliferation

Genes up-regulated in EAOC and OC: Claudin 7

Claudin 7:

- Involved in the formation of tight junctions between epithelial cells
- Tight junctions restrict lateral diffusion of lipids and membrane proteins and define the border between the apical and the basolateral compartments of epithelial cells
- Claudin enhances and stabilizes tumor cell connection and contributes to increased growth at secondary sites

Gene down-regulated in EAOC and OC: Steroidogenic acute regulatory protein (StAR)

StAR:

- Mediates the increase in pregnenolone synthesis stimulated by tropic hormones, expressed in the adrenal cortex
- Significant inverse relationship between FIGO stage and residual tumor size
- The ability of the tumor to produce progesterone could influence biological behaviour through progesterone dependent inhibition of tumor cell proliferation

Genes equally regulated in Endometriosis and EAOC: Cytokines and Growth Factors

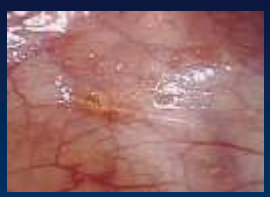
The regulation of the autoimmune system and of inflammatory cytokines is very important for the origin of endometriosis and EAOC

Genes equally regulated in EAOC and OC: StAR, SPINT1,Keratin 8, FoxM1B, FOLR1, CRABP-1, Claudin 7

- Central role in cell-cell-interaction
- Differentiation
- Cell proliferation

- Potential markers for malignat versus benign ovarian tissue and development of ovarian cancer in women with endometriosis

Case report



23 year old patient

Dysmenorrhoe
Dyspareunie
Chronic pelvic pain

Laparoscopic appearence of bladder peritoneum

Primary Peritoneal Carcinoma in a Young Women with suspected Endometriosis

Histologic appearence

Banz et al. 2009 Fertil Steril 92:390.e5-7.
Primary peritoneal carcinoma in a young women with suspected endometriosis

Conclusions

- → Endometriosis is not associated with an increased risk of cancer in general.
- → For cervical cancer, the SIR is decreased
- → The risk for uterine cancer is not changed
- → Adenomyosis is not related to an increased cancer risk.

Conclusions

- → 9 – 70% of endometrioid ovarian carcinoma or clear cell carcinoma are associated with endometriosis
- → An increased risk of ovarian cancer (endometrioid, clear-cell) has been shown for patients with endometriosis in the majority of studies

Thank you for your attention