Oncogenesis of ovarian cancer

do we understand it better?

prof. René H.M. Verheijen,
gynaecological oncologist
Ovarian cancer development:

- Origin of ovarian cancer: the tube!

- Pathways of ovarian cancer:
  - Different between early and late stage?
  - Different for different prognostic types?
  - Different for different histotypes?

- Conclusions & clinical implications
Ovarian cancer development:

- Origin of ovarian cancer: the tube!
INCENDANT OVULATION—A FACTOR IN OVARIAN NEOPLASIA?

Sir,—In these days when the pros and cons of inhibition of ovulation in women are being considered, I would like to bring to your notice some evidence of a possible relationship between the repeated involvement of the ovarian surface epithelium in the process of ovulation and the frequency of the development of the common ovarian neoplasms from this epithelium.

Compared with other mammals, the human female appears to be very excruciating with tax ova. Ovarian cycles are almost continuous from puberty to the menopause. In circumstances favourable to maximum fertility, the average number of births per married or cohabiting woman would be about twenty—an average that has not been even remotely reached in any society. Social conditions not only render the majority of ova purposeless, but also allow relatively infrequent non-ovulatory physiological rest-periods. Other mammals are more economical with their ova. Ovulations are limited to the breeding season, and may even occur only on demand after ovulation. Moreover, the reproductive potential is exercised to the full, allowing adequate physiological non-ovulatory rest-periods. In the cow (a polyoestrous animal) it is estimated that less than fifty ova are shed in a lifetime.  

Data about comparative ovarian oncology have been accumulating, 5 and three noteworthy features have been revealed. The first is that practically all tumour types encountered in the human ovary may be seen in the mammalian ovary. The second is that ovarian tumours in other mammals are apparently much rarer than in human beings. The third is that this rarity is largely due to the infrequency of epithelial neoplasms derived from the ovarian surface epithelium—the cystadenoma and the adenocarcinoma. In women these account for the majority of all ovarian neoplasms and for the great majority of ovarian malignant neoplasms.  

In the domestic fowl, with its frequent egg production, another situation has been revealed. Adenocarcinomas of the ovary is the commonest epithelial neoplasm in the whole body. 6 The relation to egg production was demonstrated in an interesting experiment where adenocarcinomas were induced in the ovaries of 17 out of 19 hens by maintaining them throughout life in a stable environment with 12 hours of fluorescent lighting daily. 7 Egg production rapidly reached a maximum, and then declined over the following 2 years, with no seasonal rest periods. No tumours appeared in central hens kept under normal lighting conditions with seasonal variations.

The surface epithelium of the ovary does not seem to play any active role in the adult processes of reproduction. 8 The few electron microscopic studies available point to a simple mesothelial function. 11, 12 Contrary to the situation in the ovary, the related surface epithelium of the testis does not show any neoplastic potentiality. The process of evolution involves repeated minor turnover to the covering epithelium. It also involves repeated exposure of the ovarian surface to the estrogen-rich viscous follicular fluid. It may be noted that local injection of estroge in the ovary capsule in mice resulted in stimulation of mitotic proliferation of the surface epithelium. 9 Ovaries of normal rats show rapid proliferation of the surface epithelium 24 hours after ovulation, and mitotic figures are concentrated near the point of ovulation. 10 Proliferation of the surface epithelium to form crypts or papillae, in mammals, was observed to be most pronounced just after ovulation. 11 In the mare, ovaulations are limited to a small area of the surface of the ovary, the ovulation fossa. 12 Ova derived from the surface epithelium have been found in that region in adult maes. 13

Epidemiological data in human beings may also be suggestive of a possible relationship between the process of ovulation and the development of the common ovarian neoplasm. In the absence of ovulation—before puberty and in patients with gonadotrophin-ovarian neoplasms of surface epithelial origin are extremely rare, while germinal and mesenchymal tumours occasionally arise. 14, 15 In patients denied the physiological rest periods afforded by pregnancies—nuns and unmarried and infertile women—a higher incidence of ovarian cancer has been reported. 16, 17 The geographical and racial incidence of ovarian cancer may be also relevant. A very low incidence of ovarian cancer has been reported in Japan, Singapore Chinese, and some South American countries, while a relatively high incidence has been reported in Scandinavian countries. 18 It is fortunate that multiple ovulation as evidenced by the frequency of double-ovum twinning is highest among Caucasians in Norway and is lowest in Japan and the yellow races (including the Mangolese Indian element in the South American population) 19 The hypothesis that the excruciating and mostly purposeless ovulations in the human female may play a contributing role in neoplasia of the surface epithelium of the ovary deserves further consideration. The implications may be vast.

Department of Obstetrics and Gynaecology, Faculty of Medicine, Amiel University, Athens, Greece.

M. F. FATHALLA.


References
In the domestic fowl, with its frequent egg production, another situation has been revealed. Adenocarcinoma of the ovary is the commonest epithelial neoplasm in the whole body. The relation to egg production was demonstrated in an interesting experiment where adenocarcinomas were induced in the ovaries of 17 out of 19 hens by maintaining them throughout life in a stable environment with 12 hours of fluorescent lighting daily. Egg production rapidly reached a maximum, and then declined over three years, with no seasonal rest periods. No tumours appeared

Cancer in tubes of chicken

Ahn e.a., Repr Biol Endocrinol 2010
Cancer of the ovary = cancer of the Fallopian tube

Molecular Evidence Linking Primary Cancer of the Fallopian Tube to BRCA1 Germline Mutations

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Journal of Pathology
DOI: 10.1002/path.1000

Original Paper

Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer

Dysplasia (only) in the tubes ……..

Piek e.a., J.Pathol. 2001, 195, 451-456
Tubal dysplasia
SEE-FIM protocol
DYSPLASTIC cells implant in ovary!

Stem cell niche in the hilum ?!

Figure 4 | Hilum cells show preferential transformation after conditional inactivation of Trp53 and Rb1. Characterization of primary OSE cells isolated from the hilum and the remainder of the ovary, and evaluated at passage 6 after Cre-IoxP-mediated inactivation of Trp53 and Rb1. a, Quantification of BrdU-positive OSE cells (n = 3, P < 0.0001, two-tailed unpaired t-test). b, c, Detection (b) and quantitative analysis (c) of senescence-associated β-galactosidase (SA-β-gal; blue) in the ovary and hilum cells (n = 3, P = 0.002, two-tailed unpaired t-test), using phase contrast microscopy. Scale bar in b, 500 μm. d, Survival of mice that were intraperitoneally transplanted with primary ovary (n = 12) and hilum (n = 8) OSE cells deficient for Trp53 and Rb1 (log-rank P = 0.0007).
Some think its from the ....... endometrium!

The origin of serous ovarian cancer may be found in the uterus: A novel hypothesis

Leon Massuger a,*, Thijs Roelofsen a, Maaike van Ham a, Johan Bulten b

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b Department of Pathology, Radboud University Nijmegen Medical Centre, The Netherlands

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UPSC: uterine papillary serous carcinoma; EIC: endometrial intraepithelial carcinoma; UPSC: uterine papillary serous carcinoma; EIC: endometrial intraepithelial carcinoma; LVSI: lymph vascular space involvement; STIC: serous tubal intraepithelial carcinoma.
Some think its from the endometrium!

Original Study

Concurrent Endometrial Intraepithelial Carcinoma (EIC) and Serous Ovarian Cancer
Can EIC Be Seen as the Precursor Lesion?

Thijs Roelofsen, MD,* Léon C.L.T. van Kempen, PhD,† Jeroen A.W.M. van der Laak, PhD,† Maaikje A. van Ham, MD, PhD,* Johan Bulten, MD, PhD,† and Leon E.A.G. Massuger, MD, PhD*

Objective: The pathogenesis of serous ovarian carcinoma (SOC) is still unknown. Recently, endometrial intraepithelial carcinoma (EIC) was proposed to be the precursor lesion of SOC. This study examines the model of EIC as precursor for SOC.

Methods: Cases of SOC with a noninvasive or superficially invasive serous lesion, a hyperplastic lesion with/without atypia, or EIC in the endometrium were selected for inclusion in this study. Tissue sections from both ovaries, the fallopian tubes, and the uterine cervix were extensively reviewed by an expert gynecopathologist. For both EIC and SOC, immunostaining for p53, Ki-67, estrogen receptor, and progesterone receptor; TP53 mutation analysis; and in situ ploidy analysis were performed.

Results: Nine cases of SOC with concurrent EIC in the endometrium were identified. Immunostaining for p53, Ki-67, estrogen receptor, and progesterone receptor revealed almost identical expression patterns and similar intensities in each pair of EIC and coincident SOC. Identical TP53 mutations were found in SOC and coinciding EIC in 3% of the cases, suggesting a clonal origin. DNA ploidy analysis, as a marker for neoplastic progression, demonstrated an increased number of aneuploid nuclei in SOC compared to their corresponding EIC (P = 0.039). In addition, the mean amount of DNA per nucleus in SOC was higher (ie, more aneuploid) compared to EIC (P = 0.039).

Conclusion: This study provides a first indication of EIC as possible precursor lesion for SOC. This finding could have major clinical implications for future ovarian cancer management and underscores EIC as a possible target for early SOC detection and prevention.

Key Words: Endometrial intraepithelial carcinoma, Ovarian carcinoma, Lesion of origin, Precursor

Received August 19, 2011, and in revised form October 15, 2011. Accepted for publication November 22, 2011.

(Int J Gynecol Cancer 2012;00: 00–00)
(epi)genetically different

Tubal pre-malignancy:
- Tubes: 27%
- Ovaries: 9%

Genetically different:
- USPC
- TSPC
- OSPC

Gains
Losses

Piek, 2001
Seeber, 2010
What happens in BRCA-mutation carrier:

carcinogenesis in BRCA1/BRCA2 mutation carriers
Fallopian tube carcinogenesis

- Normal
- p53 signature
- TIC
- Serous Ca

Genotoxic damage (ovulation)
DNA strand breakage
Cell cycle arrest
P53 mutation

Additional genetic disturbances
Cell cycle activation
Proliferation
Early malignant phenotype

Tumor expansion
Exfoliation
Peritoneal/ovarian seeding
Metastasis

Crum e.a. Curr Opin Gynecol 2007
from serous cell outgrowth (SCOUT) to serous tubal intra-epithelial carcinoma (STIC)

Byron e.a., Modern Pathol, 2012
DYSPLASTIC cells implant in ovary!
Prophylactic bilateral salpingo-oophorectomy

Piek e.a., *J.Pathol.* 2001, 195, 451-456
Pap-smear for ovarian cancer
Pap-smear for ovarian cancer ???????????

First 10 patients done, laparo- and hysteroscopically!

Kinde e.a., Sci Trans Med 2013; Lum e.a., Min Invasive Gynecol 2014
Salpingectomy only ..........

Does Bilateral Salpingectomy with Ovarian Retention Warrant Consideration as a Temporary Bridge to Risk-Reducing Bilateral Oophorectomy in BRCA1/2 Mutation Carriers?

Mark H. GREENE, M.D.,
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Division of Gynecologic Oncology, Yale University School of Medicine, New Haven, CT 06520

The tubal hypothesis of ovarian cancer: caution needed
However, despite the temptation to patients and doctors to rapidly translate the tubal hypothesis into clinical practice, we believe that it is too early to support a staged approach to surgical prevention of ovarian cancer and that RRSO should remain the optimum strategy.
**Trial:**
Radical Fimbriectomy for Young BRCA Mutation Carriers

1. Women are allowed to enter the trial even if they have had breast cancer.

2. Entrants have to be “unprepared” to undergo bilateral oophorectomy (although it is not clear what “unprepared” means in this context).

3. The study is not due to be completed until 2019.

Leblanc, Lille, 2011
Ovarian cancer development:

- Origin of ovarian cancer: the tube!

- Pathways of ovarian cancer:
  - Different between early and late stage?
  - Different for different prognostic types?
  - Different for different histotypes?
Genetic differences early & late stage

Zaal e.a., Cell Onc 2012
Copy number profiles: ovarian cancer vs glioblastoma

Amplified (red) & Deleted (blue) chromosome arms

Amplified Red) & Deleted (blue) regions

The Cancer Genome Atlas Research Network (TCGA)

Copy number profiles:
ovarian cancer vs glioblastoma

Amplified (red) & Deleted (blue)
Chromosome arms

Amplified Red) & Deleted (blue) regions

Genomic dynamics

Hoogstraat e.a., 2014
Vaughan e.a., Nature Reviews Cancer, 2011
Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations.

- **Epithelial**
  - High-grade serous
    - TP53, BRCA1, NF1, RB1, CDK12
  - Low-grade serous
    - BRAF, KRAS, NRAS, ERBB2
  - Mucinous
    - KRAS, HER2 amplification
  - Clear cell
    - ARID1A, PIK3CA, PTEN, CTNNB1, PPP2R1α
  - Endometrioid
    - ARID1A, PIK3CA, PTEN, PPP2R1α

- **Nonepithelial**
  - Sex cord-stromal
    - Granulosa cell: FOXL2
    - Granulosa cell: Sertoli-Leydig cell: Dicer1
  - Others, including germ cell
    - MMR deficiency

Pathway alterations:
- PI3K/RAS/NOTCH/FOXO1

* CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.

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Targeted therapies in ovarian cancer.

And other pathways

Response of xenografts to conventional chemotherapy +/- notch inhibitor (MRK-003/GSI)

Platinum sensitive

Platinum resistant

Groeneweg e.a., in prep.
Pathways to mucinous and serous ovarian cancer

Transport of salpingeal epithelium

Conversion of OSE

Mullerian inclusion

HOX10

P53 mutation (rare)

P53 signature (rare)

HOX11

mucinous cystadenoma

K-ras

borderline mucinous cystadenoma

Mucinous cystadenocarcinoma

High Grade serous cystadenocarcinoma

Low Grade serous cystadenocarcinoma

borderline serous cystadenoma

serous cystadenoma

K-ras

Jarboe, Histopathol, 2008
Oncogenesis: two pathways

*Kurman e.a. / Crum e.a.*

**Borderline tumour**
(Atypical Proliferative Serous Tumour) (MicroPapillary Serous Carcinoma)

**Ovary**

- KRAS
- BRAF

**Inclusion cyst**

- p53 (e.a.)

**Cancer**

- Type I
- Type II

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*After Kurman e.a., 2008*
• **Type 1**
  
  a) Slowly growing, limited extension, genetically stable
  
  b) Low grade serous, mucinous, endometrioid, clear cell
  
  c) Mutations in KRAS, BRAF, PTEN, and beta-catenin

• **Type 2**
  
  a) Aggressive, fast growing, genetically instable
  
  b) High Grade, malignant mixed mesodermal tumours, undifferentiated tumours
  
  a) Mutation in P53

Shih I, Kurman RJ. J Pathol 2004
Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis

Robert J. Kurman, MD; Kala Visvanathan, MB, BS, FRACP, MHS; Richard Roden, PhD; T. C. Wu, MD, PhD; Ie-Ming Shih, MD, PhD
Pathways to mucinous and serous ovarian cancer

- Transport of salpingeal epithelium
- Conversion of OSE
  - HOX10
  - P53 mutation (rare)
  - P53 signature (rare)
- HOX11
- Mullerian inclusion
- K-ras
  - borderline mucinous cystadenoma
  - Mucinous cystadenocarcinoma
- Serous cystadenoma
  - High Grade serous cystadenocarcinoma
  - Low Grade serous cystadenocarcinoma
- Borderline serous cystadenoma

Jarboe, Histopathol, 2008
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**MLPA results**

Green = gain  Red = loss

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</table>

**Nowee/Verbruggen e.a., 2009**
Mutated BRAF plays a role in:
- Melanoma
- Lung cancer
- Colorectal cancer
- Thyroid cancer
- Ovarian cancer
Gel analysis after PCR

11 / 27 serous BTOs (40%): V599E mutation

Verbruggen/Sieben, 2008
Gel analysis after PCR

11 / 27 serous BTOs (40%): V599E mutation

*BRAF + NOT in serous carcinoma’s*
Pathways to mucinous and serous ovarian cancer

Transport of salpingeal epithelium

Conversion of OSE

HOX10

Mullerian inclusion

P53 mutation (rare)

P53 signature (rare)

serous cystadenoma

HOX11

mucinous cystadenoma

borderline mucinous cystadenoma

BRAF K-ras

borderline serous cystadenoma

High Grade serous cystadenocarcinoma

Low Grade serous cystadenocarcinoma

Mucinous cystadenocarcinoma

K-ras

borderline mucinous cystadenoma

Jarboe, Histopathol, 2008
Oncogenesis: three pathways
Verheijen/Verbruggen/Nowee/van Diest e.a.

Mucinous BTO
Cystadenoma
Ovary
Inclusion cyst

Serous BTO
BRAF
KRAS
APST
(Atypical Proliferative Serous Tumour)
MPSC
(MicroPapillary Serous Carcinoma)

Cancer
Type I
Type II

p53
(e.a.)

After Kurman e.a., 2008

© Verbruggen / Verheijen
Conclusions

- Ovarian carcinoma arises from tubal (serous) epithelium
  - For prevention: the tube more important than the ovary
Conclusions

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• Ovarian carcinoma is NOT a single entity
  – Individualized treatment warranted
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  – Implications for detection and treatment
Conclusions

• Ovarian carcinoma arises from tubal (serous) epithelium
  – For prevention: the tube more important than the ovary

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  – Individualized treatment warranted

• Type I and II tumours have distinguished pathways
  – Implications for detection and treatment

• Borderline tumours have distinct pathways
  – Borderline tumors should not be treated as cancer
Hens for a model .......

ADENO-CARCINOMATA IN HENS KEPT IN A CONSTANT ENVIRONMENT

J. E. WILSON

Ministry of Agriculture, Fisheries and Food Veterinary Laboratory, Lasswade, Scotland

Adenocarcinomata were present in 17 of 19 hens maintained in a climatic chamber from hatching and there is strong presumptive evidence that the condition was also responsible for the stricture of the duodenum which gave rise to the massive alimentary impaction which caused the first death. The first evidence of illness was detected 784 days after the start of the experiment. Typically affected birds appeared off colour and moping and when handled the abdomen was tense. As the disease progressed distension of the abdomen was prominent and bodily condition was lost leading finally to gross emaciation. The duration of illness was up to 500 days or more.

Adenocarcinomata were present in the ovaries of 16 and the oviducts of 17 of the 18 birds which died. There were metastases in the liver in six cases, in the spleen in two cases and the kidneys and lungs in one. Tumours in the oviduct were always larger than those in the ovary but in almost every case the most striking pathological feature was the gross abnormality of the intestinal tract.

In the earliest cases this consisted of contraction and distortion of the duodenum; in advanced cases the intestines were adhesed into a solid mass, sometimes resulting in massive impaction of the proventriculus and gizzard. Ascites was commonly present with up to more than 500 ml. of fluid in the peritoneal cavity.
Hens for a model ..........
Histologische und elektronenmikroskopische Untersuchungen zur Adenokarzinomatosose der Legehenmen

G. Behmann und V. Bergmann

Mit 11 Abbildungen

(Eingegangen am 2. Januar 1975)


In dieser Arbeit soll dagegen eine ausführlichere, die pathohistologische Diagnose unterstützende Darstellung der morphologischen Charakteristika gegeben und zu ihrer histogenese Stellung genommen werden.

Eigene Untersuchungen

Material und Methodik

Lee et al., 2007
Begriffsbestimmungen

**STIC**
- Erhöhte nuclear / Zytoplasma ratio
- nuclear pleomorphism
- Desorganisiertes wachsen
- Erhöhte mitosen
- Abwesenheit von Flimmerepithel
- Anwesenheit von große nucleoli

**P53 signature**
- Starke nuclear Färbung (Verdunklung von nuclear detail)
- Mehr als 12 nebeneinander liegenden nuclei
- **Morphologisch normal epithel**

Shaw et al., 2009

Lee et al., 2007
• P53 Äußerung wurde observiert im TIC, aber auch im beginne eileiter epithelium ("p53 signatures")
• P53 mutations wurde gesehen im 100% aller TIC und 57% von p53 signatures
• Inzidenz von p53 signatures vergleichbar zwischen hohes risiko frauen und controls (38% gegen 33%) (Lee 2007, Folkins 2008)

• Im einem fall wurde ein gleiche p53 mutation im signature und seröze peritoneal krebs gefunden. (Carlson 2008)

• P53 signatures wurden nicht gefunden im cortical inclusion Zyste.
Crum et al.

- Im BRCA mutation positive Frauen hängen p53 signatures fest an bekannte Risiko Faktoren für ovarial Krebs: wenig Kinder, hohes alter am ersten Geburt (Saleemuddin 2008)

- Beides TIC und p53 signatures wurde auch gefunden im Frauen mit Gebärmutter krebs (Jarboe/Miron 2009, Jarboe/Pizer 2009)

- P53 signatures im fimbriae wurden oft gefunden im Frauen mit Li-Fraumeni syndrome (Xian 2010)
Development of LG & HG Serous carcinoma

Kurman, Am J Surg Pathol., 2010
Development of endometrioid and clear cell carcinoma

Kurman, 2010
Pathways to mucinous and serous ovarian cancer

Transport of salpingeal epithelium

Conversion of OSE

HOX10

Mullerian inclusion

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Jarboe, Histopathol, 2008
Pathways to mucinous and serous ovarian cancer

- Transport of salpingeal epithelium
- Conversion of OSE
- Mullerian inclusion

**MUCINOUS CANCER PATHWAYS**

- HOX10
- P53 mutation (rare)
- K-ras

- HOX11

- HOX11 -> mucinous cystadenoma
- K-ras -> borderline mucinous cystadenoma

**SEROUS CANCER PATHWAYS**

- HOX10
- P53 signature (rare)
- K-ras

- HOX11

- HOX11 -> serous cystadenoma
- K-ras -> borderline serous cystadenoma

**MUCINOUS CARCINOMA**

- Mucinous cystadenocarcinoma

**SEROUS CARCINOMA**

- High Grade serous cystadenocarcinoma
- Low Grade serous cystadenocarcinoma

Jarboe, Histopathol, 2008
Fallopian tube carcinogenesis

Fimbria

- Benign tubal Secretory cell
- P53 signature
- TIC
- Serous carcinoma
- Metastatic serous carcinoma

Ovary

- Endosalpingiosis
- Ovarian surface epithelium (Secretory/ciliated)
- Cortical inclusion cyst
- Endometrioma
- Cystadenoma
- Borderline cystadenoma
- Cystadenocarcinoma (mucinous, endometrioid, serous (less common))
Genomic aberrations relate early and advanced stage ovarian cancer

Comparative Genomic Hybridization
Flat – cuboidal cells
Flat – cuboidal cells

Inclusion and METAPLASIA

Serous and ciliated cells
Inclusion-metaplasia theory

Flat – cuboidal cells → Inclusion and METAPLASIA → Serous and ciliated cells

dysplasia → carcinoma