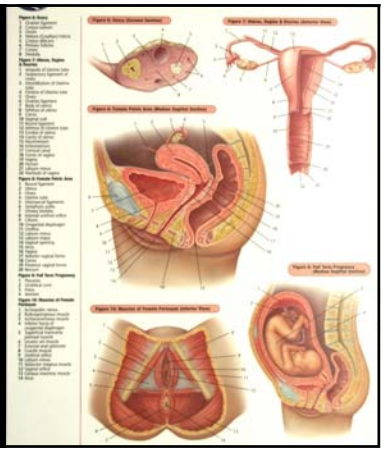
Common neoplasms of the cervix, uterus, and ovaries

Ie-Ming Shih, MD, PhD

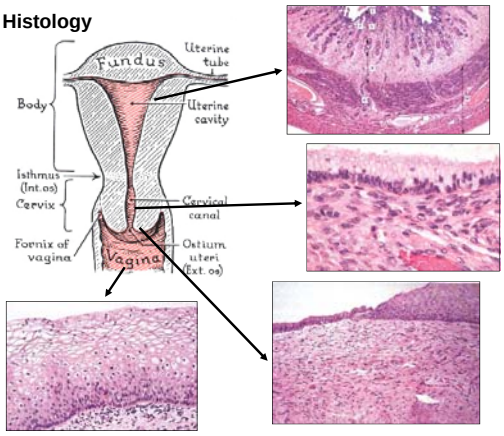
http://pathology2.jhu.edu/shihlab/index.cfm

March 25, 2015

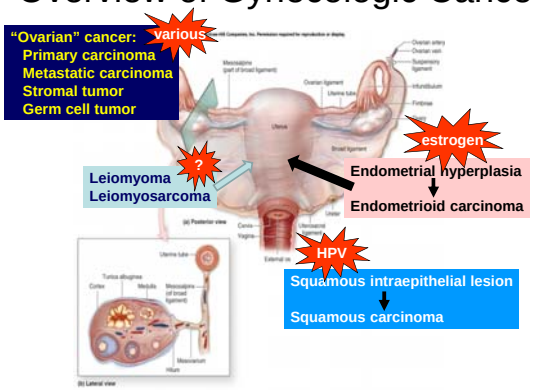
Review of anatomy



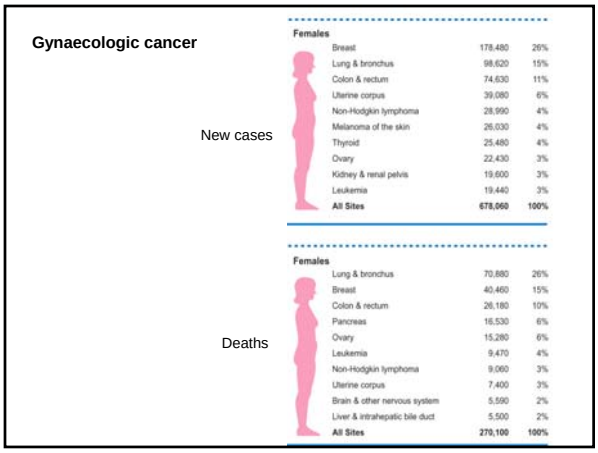
Histology



Overview of Gynecologic Cancer



Gynaecologic cancer



Cancer statistics

http://CAonline.AmCancerSoc.org

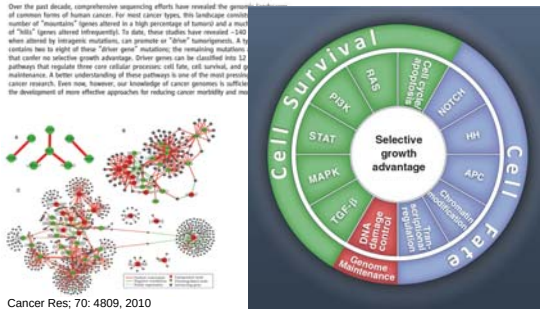
	New cases	Deaths
Endometrial cancer	39,080	7,400
Ovarian cancer	22,430	15,280
Cervical cancer	11,150	3,670
Vulva cancer	3,490	880
Vaginal cancer and others	2,140	790

CANCERGENOMICS

REVIEW

Science 339: 1546, 2013

Cancer Genome Landscapes



Cancer Res; 70: 4809, 2010

ARTICLE

OPEN

Integrated genomic characterization of endometrial carcinoma

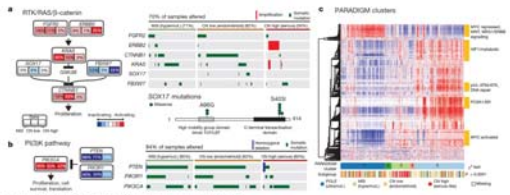


Figure 4 | Pathway alterations in endometrial carcinomas. a, The RTK/RAS/β-catenin pathway is altered through several mechanisms that exhibit mutually exclusive patterns. Alteration frequencies are expressed as a percentage of all cases. The right panel shows patterns of occurrence. b, The PI3/K pathway has mutually exclusive *PIK3CA* and *PIK3R1* alterations that

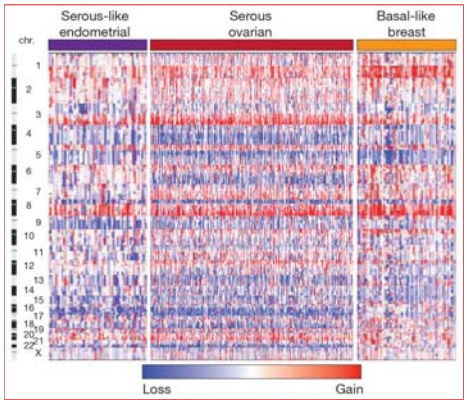
ARTICLE

doi:10.1038/nature10166

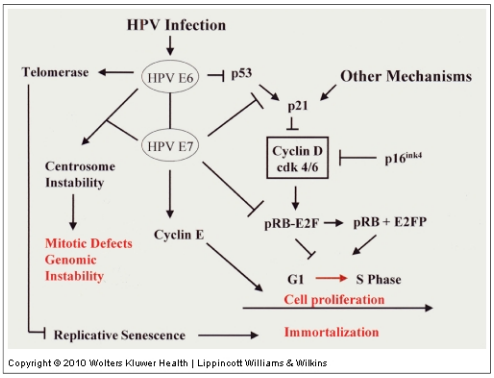
Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

A catalogue of molecular aberrations that cause ovarian cancer is critical for developing and deploying therapies that will improve patients' lives. The Cancer Genome Atlas project has analysed messenger RNA expression, microRNA expression, promoter methylation and DNA copy number in 489 high-grade serous ovarian adenocarcinomas and the DNA sequences of exons from coding genes in 316 of these tumours. Here we report that high-grade serous ovarian cancer is characterized by *TP53* mutations in almost all tumours (96%); low prevalence but statistically recurrent somatic mutations in nine further genes including *NF1*, *BRCA1*, *BRCA2*, *RB1* and *CDK12*; 113 significant focal DNA copy number aberrations; and promoter methylation events involving 168 genes. Analyses delineated four ovarian cancer transcriptional subtypes, three microRNA subtypes, four promoter methylation subtypes and a transcriptional signature associated with survival duration, and shed new light on the impact that tumours with *BRCA1*/*BRCA2* (*BRCA1* or *BRCA2*) and *CCNE1* aberrations have on survival. Pathway analyses suggested that homologous recombination is defective in about half of the tumours analysed, and that *NOTCH* and *FOXM1* signalling are involved in serous ovarian cancer pathophysiology.



Cervical/vaginal/vulvar lesions and carcinomas



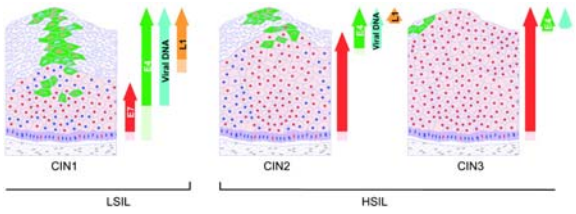

BOOKS ET AL.

Of HeLa and Human Lives

65860 articles

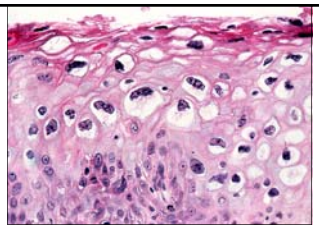
March 23, 2011

The expression of viral proteins changes in a predictable way during cancer progression

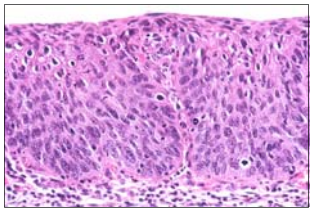


Middleton, K. et al. 2003. J. Virol. 77(19):10186-10201

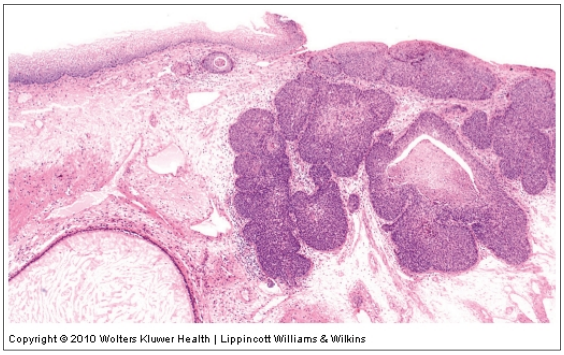
Journal of Virology



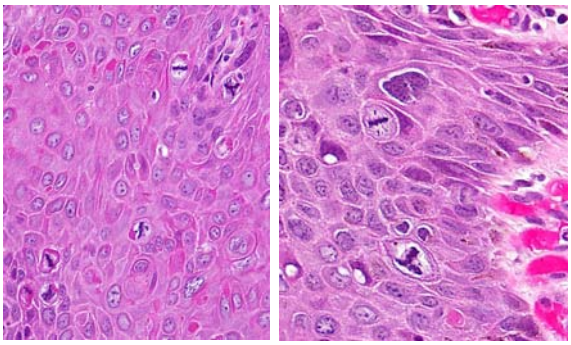
Low-grade lesion

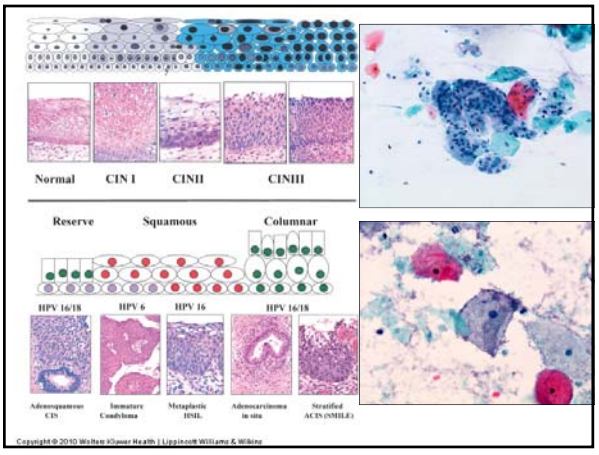


High-grade lesion



HPV-induced chromosomal instability





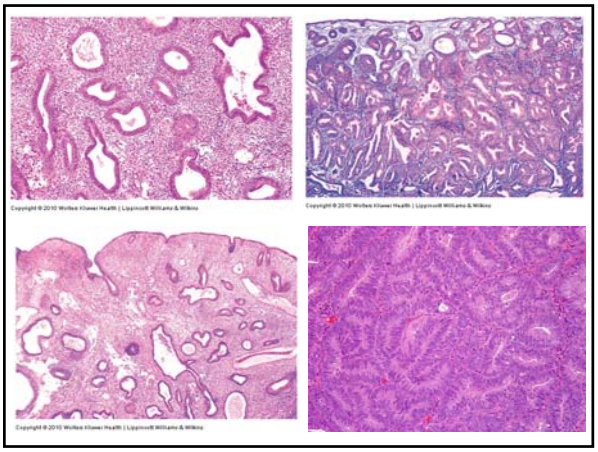
Uterine carcinoma

Uterine endometrioid carcinoma (type I)

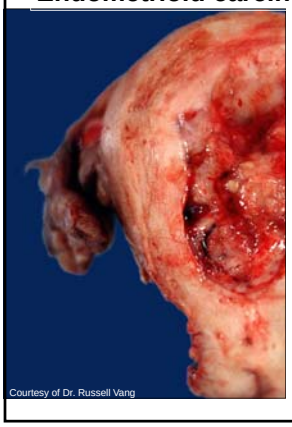
Age: younger (35-65 y/o)
Stage: early, curable
Precursor: endometrial hyperplasia
Etiology: unopposed estrogen stimulation
Molecular genetics: Wnt, PIK/Pten, Kras
MSI or CIN: MSI

Uterine serous carcinoma (type II)

Age: older (> 65 y/o)
Stage: advanced, mostly incurable
Precursor: EIC in the background of atrophy and endometrial polyp
Etiology: unknown
Molecular genetics: p53, PP2A
MSI or CIN: CIN



Endometrioid carcinoma of the uterus



Pten

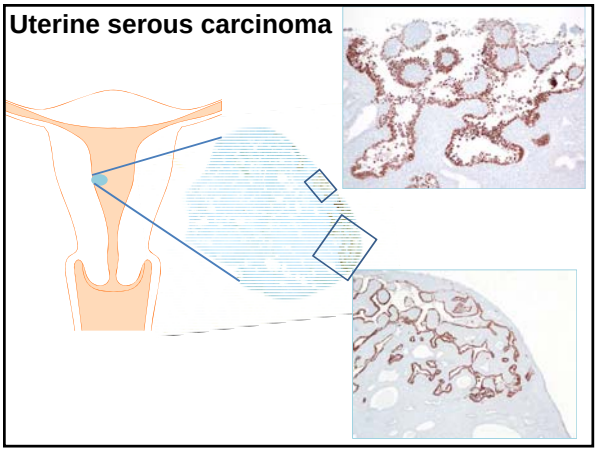
β-catenin

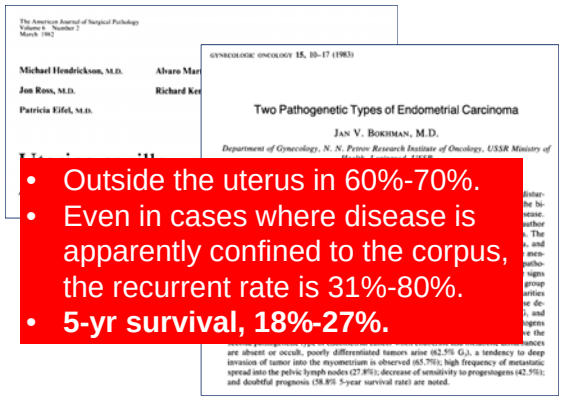
PIK3CA

KRAS

microsatellite instability

Uterine serous carcinoma

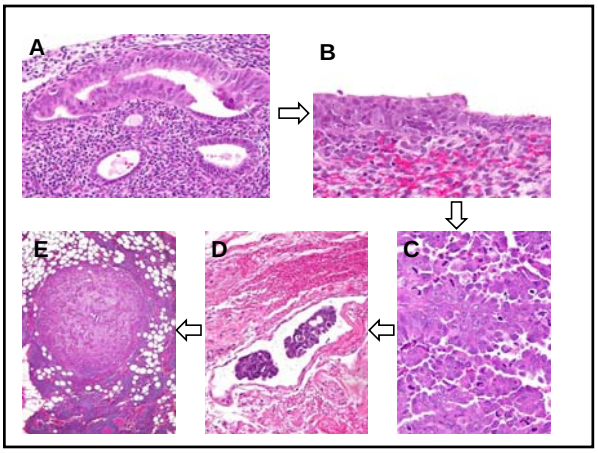


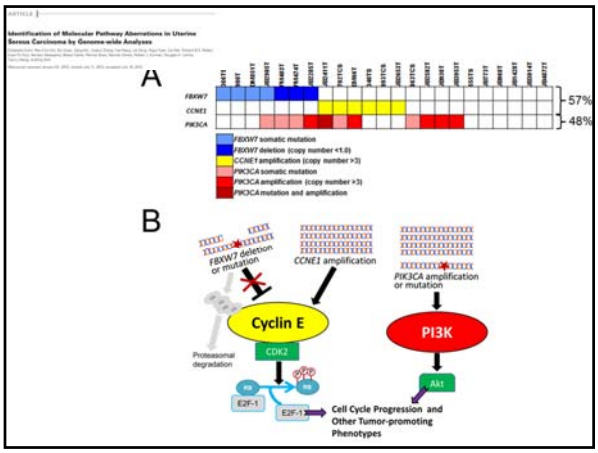


Two Pathogenetic Types of Endometrial Carcinoma

Jan V. Bokhman, M.D.

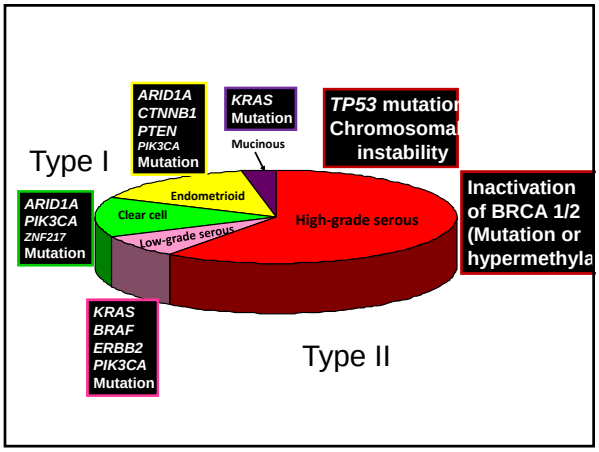
- Outside the uterus in 60%-70%.
- Even in cases where disease is apparently confined to the corpus, the recurrent rate is 31%-80%.
- **5-yr survival, 18%-27%.**



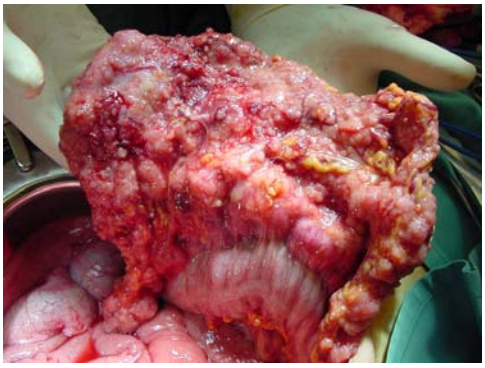


The fact of ovarian cancer

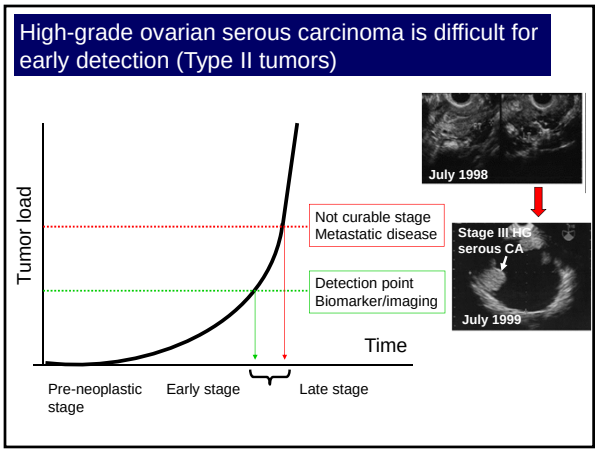
- Ovarian carcinoma is the major disease of cancer mortality in women (22,430 new cases 15,280 new deaths in 2007)
- Molecular etiology is poorly understood
- Patients are usually on death roll if tumors recur
- A peritoneal disease, ideal for i.p. therapy



Molecular genetic analysis of HGSC

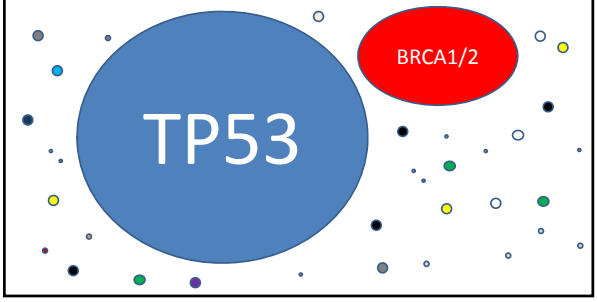


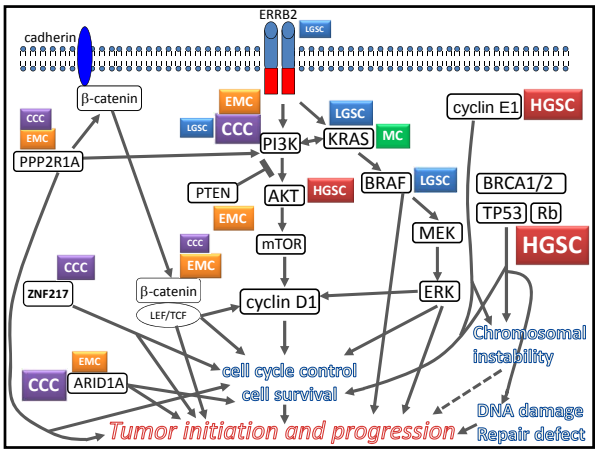
High-grade ovarian serous carcinoma is difficult for early detection (Type II tumors)

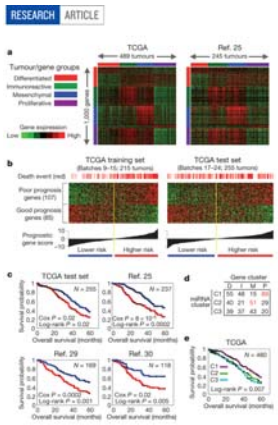


TCGA: high-grade serous carcinoma

Somatic mutations found in TCGA



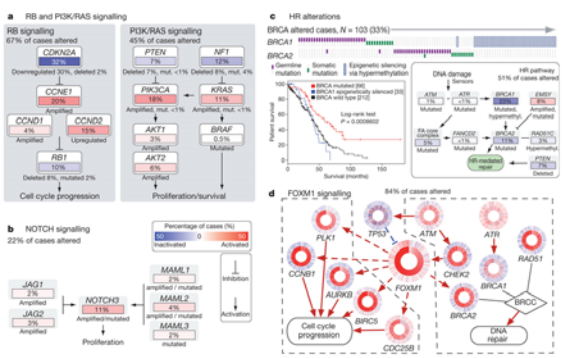


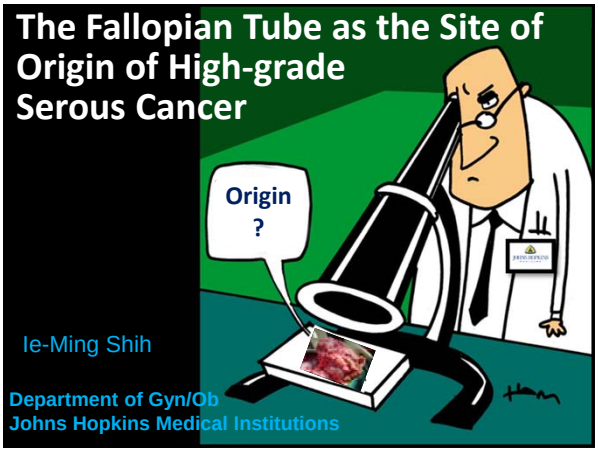


TCGA- molecular subtypes based on genes and miRNA expression patterns and outcome prediction in high-grade serous carcinoma

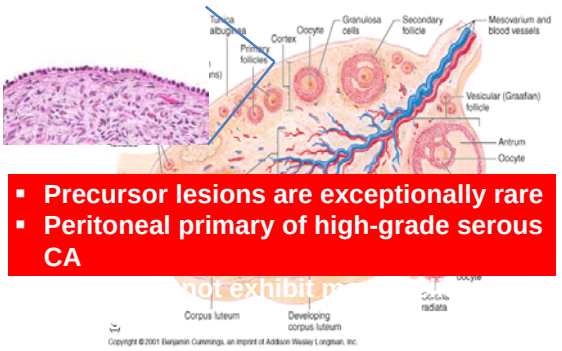
- 4 transcriptional subtypes
- 3 miRNA subtypes
- 4 methylation subtype

TCGA- Major pathway analysis

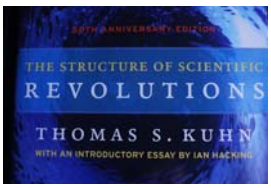




OSE as the origin of high-grade serous carcinoma

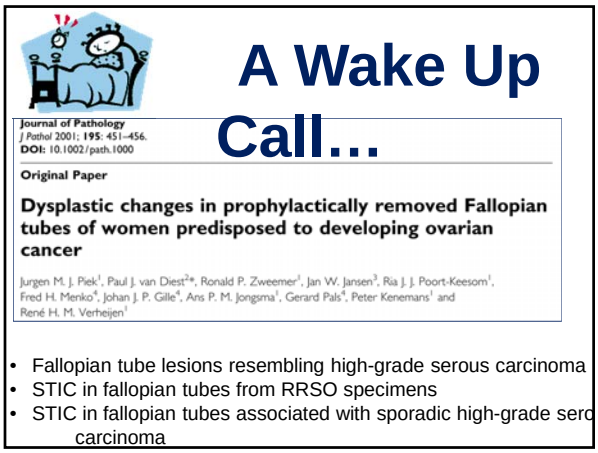


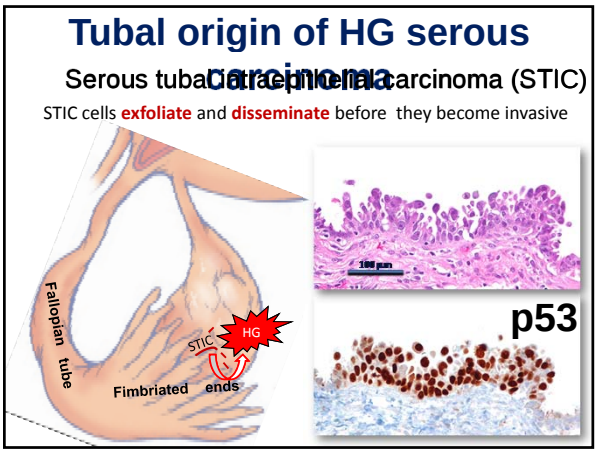
- **Precursor lesions are exceptionally rare**
- **Peritoneal primary of high-grade serous CA**

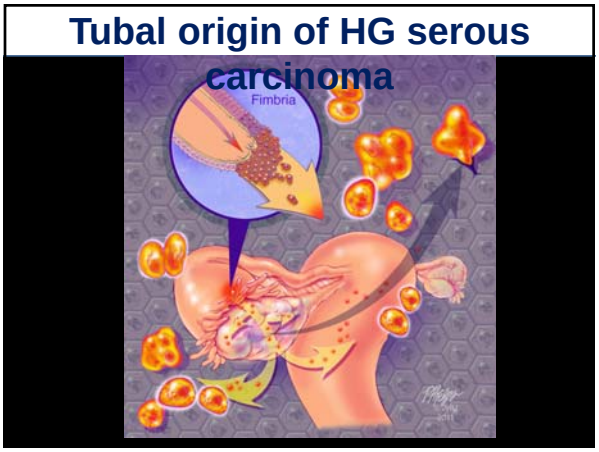


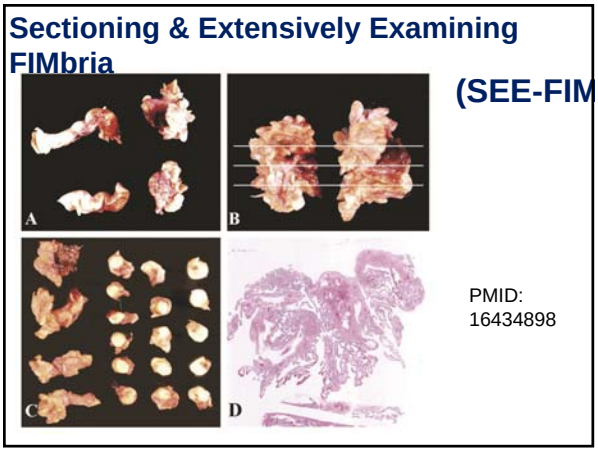
The birth of a new paradigm

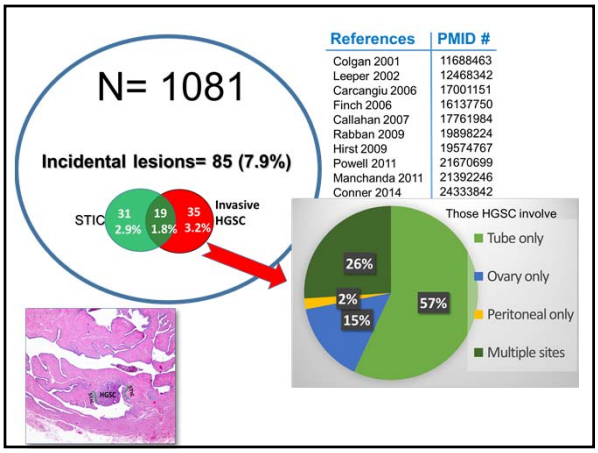
When puzzles arise that repeatedly resist solutions a ***crisis of confidence*** occurs. During a crisis, the paradigm is subjected to testing and might be rejected. If that occurs, a new **paradigm** replaces the previous one and a ***scientific revolution*** has occurred

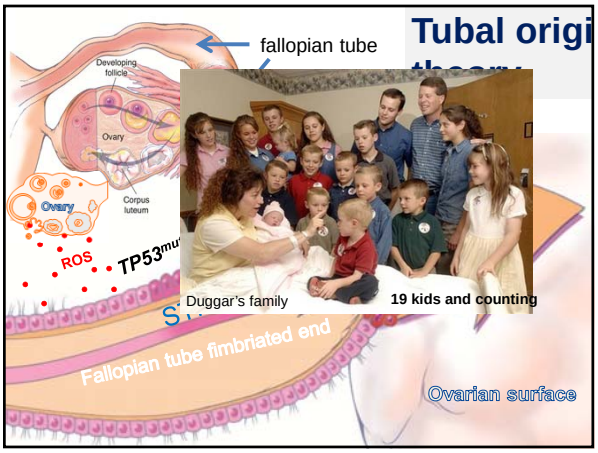

A Wake Up Call…
Journal of Pathology
J Pathol 2001; 195: 451–456.
DOI: 10.1002/path.1000
Original Paper
Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer
Jurgen M. J. Piek, Paul J. van Diest*, Ronald P. Zweemer, Jan W. Jansen, Ria J. J. Poort-Keesom, Fred H. Menko, Johan J. P. Gille, Ans P. M. Jongsma, Gerard Pals, Peter Kenemans and René H. M. Verheijen
• Fallopian tube lesions resembling high-grade serous carcinoma
• STIC in fallopian tubes from RRSO specimens
• STIC in fallopian tubes associated with sporadic high-grade sero
carcinoma

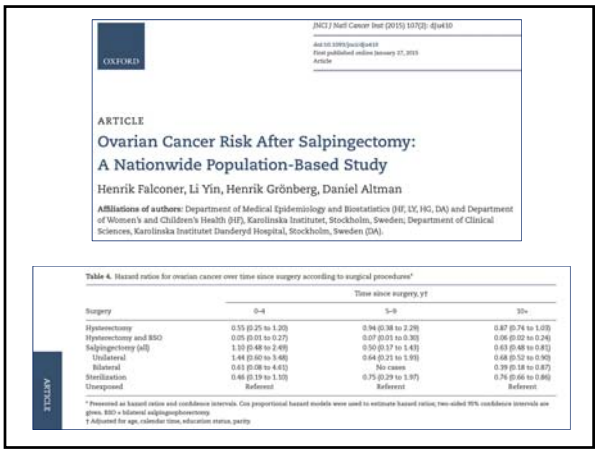

Tubal origin of HG serous carcinoma
Serous tubal intraepithelial carcinoma (STIC)
STIC cells exfoliate and disseminate before they become invasive
Fallopian tube
STIC
HG
Fimbriated ends
p53


Tubal origin of HG serous carcinoma
Fimbria


Sectioning & Extensively Examining FIMbria
(SEE-FIM
A
B
C
D
PMID: 16434898


N= 1081
Incidental lesions= 85 (7.9%)
STIC
31 2.9%
19 1.8%
35 3.2%
Invasive HGSC
References
PMID #
Colgan 2001 11688463
Leeper 2002 12468342
Carcangiu 2006 17001151
Finch 2006 16137750
Callahan 2007 17761984
Rabban 2009 19898224
Hirst 2009 19574767
Powell 2011 21670699
Manchanda 2011 21392246
Conner 2014 24333842
Those HGSC involve
Tube only
Ovary only
Peritoneal only
Multiple sites
26%
2%
15%
57%


fallopian tube
Tubal origi
Developing follicle
Ovary
Corpus luteum
ROS
Duggar's family
19 kids and counting
Fallopian tube fimbriated end
Ovarian surface



ARTICLE

Ovarian Cancer Risk After Salpingectomy: A Nationwide Population-Based Study

Henrik Falconer, Li Yin, Henrik Grönberg, Daniel Altman

Affiliations of authors: Department of Medical Epidemiology and Biostatistics (HF, LY, HG, DA) and Department of Women's and Children's Health (HF), Karolinska Institutet, Stockholm, Sweden; Department of Clinical Sciences, Karolinska Institutet Danderyd Hospital, Stockholm, Sweden (DA).

Table 4. Hazard ratios for ovarian cancer over time since surgery according to surgical procedure*

Surgery	Time since surgery, yr 0–4	5–9	10+
Hysterectomy	0.55 (0.25 to 1.20)	0.94 (0.38 to 2.29)	0.87 (0.74 to 1.03)
Hysterectomy and BSO	0.05 (0.01 to 0.27)	0.07 (0.01 to 0.30)	0.06 (0.02 to 0.24)
Salpingectomy (all)	1.10 (0.48 to 2.49)	0.50 (0.17 to 1.43)	0.63 (0.48 to 0.81)
Unilateral	1.44 (0.60 to 3.48)	0.64 (0.21 to 1.93)	0.68 (0.52 to 0.90)
Bilateral	0.61 (0.08 to 4.61)	No cases	0.39 (0.18 to 0.87)
Sterilization	0.46 (0.19 to 1.10)	0.75 (0.29 to 1.97)	0.76 (0.66 to 0.86)
Unexposed	Referent	Referent	Referent

* Presented as hazard ratios and confidence intervals. Cox proportional hazard models were used to estimate hazard ratios; two-sided 95% confidence intervals are given. BSO = bilateral salpingo-oophorectomy.
† Adjusted for age, calendar time, education status, parity.

ARTICLE

STICs in > 50% of HGSCs and in ~5-10% of fallopian tubes removed prophylactically.

STICs were only associated with serous CA but rarely with other types of gynecologic cancers.

HGSC expresses markers of fallopian tube epithelium not OSE.

HGSC rarely presents as stage I disease; screening for early HGSC did not work.

Human Cancer Biology Clin Cancer Res 2005, 11:6116

Patterns of Gene Expression in Different Histotypes of Epithelial Ovarian Cancer Correlate with Those in Normal Fallopian Tube, Endometrium, and Colon

Rebecca T. Marquez,[1] Keith A. Baggerly,[2] Andrea P. Patterson,[1] Jinsong Liu,[5] Russell Broaddus,[6] Michael Frumovitz,[3] Edward N. Atkinson,[2] David I. Smith,[6] Lynn Hartmann,[6] David Fishman,[7] Andrew Berchuck,[8] Regina Whitaker,[8] David M. Gershenson,[3] Gordon B. Mills,[4] Robert C. Bast, Jr.,[1] and Karen H. Lu[3]

Carcinoma	Normal ovary	Fallopian tube	Colon	Endometrium
Clear cell	0.9623	0.7791	0.6775	**0.0002**
Endometrioid	0.4915	0.5928	0.9748	**0.0172**
Serous	0.0743	**0.0042**	0.9993	0.8504
Mucinous	0.6905	0.4863	**0.0003**	0.9860

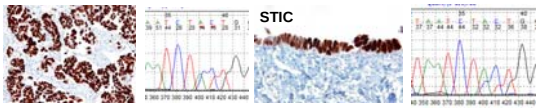
rank-sum analysis

Identical *TP53* mutations in STIC & concurrent high-grade serous carcinoma

Journal of Pathology
J Pathol 2012; 226: 421–426
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.3023

ORIGINAL PAPER

TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions



Identical mutations in 27/29 pairs

Significance of telomere shorte

Vol. 10, 3317–3326, May 15, 2004 Clinical Cancer Research 3317

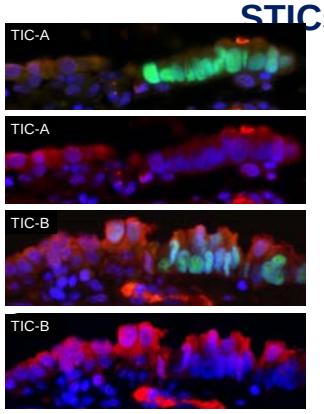
Telomere Length Abnormalities Occur Early in the Initiation of Epithelial Carcinogenesis

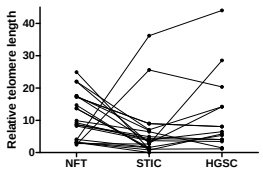
Urinary bladder, esophagus, large intestine, oral cavity, uterine cervix, breast: 97% with telomere length abnormality most of them are shortening.

Telomere Shortening Occurs Early During Breast Tumorigenesis: A Cause of Chromosome Destabilization Underlying Malignant Transformation?

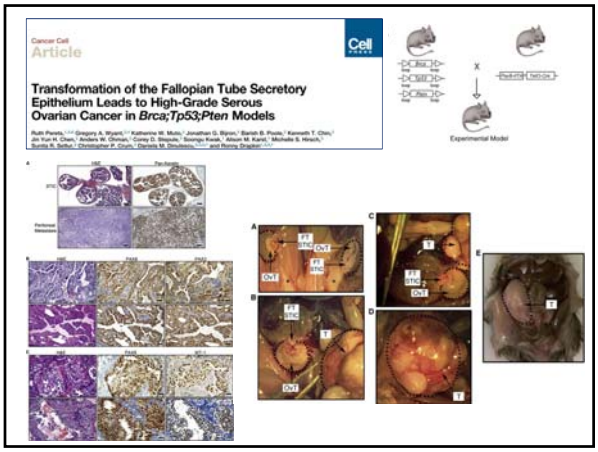
Alan K. Meeker[1,2,3] and Pedram Argani[1]

Shorter telomere length in most STICs

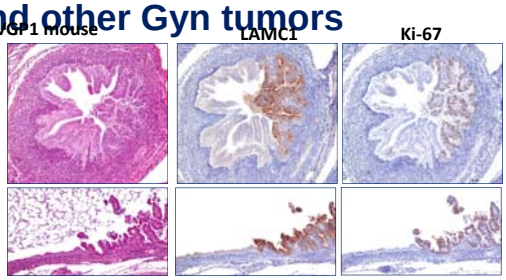




Am J Surg Pathol, 34:829, 2010



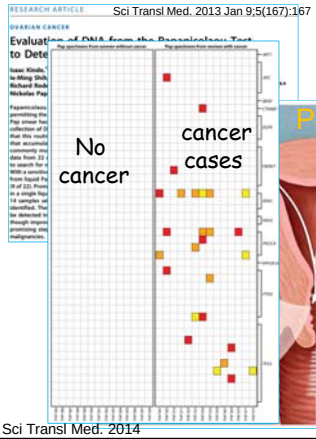
OVGP-1 T-Ag mouse spontaneously develops STIC and other Gyn tumors



J Pathol, 233:228, 2014

Summary so far

- STIC & HGSC are always clonally related
- STIC expresses HGSC markers
- Precursor lesions of STIC may exist
- As compared to HGSC, STIC has shorter telomere, lower level of centrosome amplification & reduced ALDH1A1 exp
- Mouse models- developing STIC then ovarian cancer



DNA from most endometrial and a fraction of ovarian cancers can be detected in a standard liquid-based Pap smear specimen obtained during routine pelvic examination

Sci Transl Med. 2014

Things to remember…

1. All the female reproductive tract and organs including placenta can give rise to neoplastic diseases. Some are common and some are rare!
2. The most common neoplasm among gynecologic tumors is leiomyoma (smooth muscle tumors from myometrium in the uterus) which causes pain, bleeding and infertility in women. Not much research is going on.
3. Endometri**oid** carcinoma is the most common malignant tumors in the uterus. Most of cases are at early stages and prognosis is excellent. This type of cancer arises from precursors, endometrial hyperplasia and is characterized by defined mutations in PTEN and beta-catenin genes.

Things to remember…

4. Ovarian "cancer" is a heterogeneous group of tumors and can be broadly classified into primary epithelial, stromal, germ cell and metastatic tumors.
5. Within the primary epithelial tumors, they can be classified into different histologic subtypes and each subtype can have benign, borderline or malignant categories.
6. Different histologic subtypes have unique molecular pathways for their development and progression. So, study of ovarian cancer should separate different histological types.

Things to remember…

7. The high-grade serous carcinoma is what has been referred as “ovarian cancer”. It is the most common and lethal type of all ovarian neoplasms.

8. The origin of “ovarian” cancer is still not known. Increased ovulation (causes surface inclusion bodies) is a risk factor…A new hypothesis of tubal origin has been recently proposed.

9. Early detection of high-grade serous carcinoma may not work… Focus on the studies of recurrent tumors may likely have a translational impact.