Ovarian Cancer: The New Paradigm

(and what you need to know clinically)

Dianne Miller, M.D., FRCSC
University of British Columbia
and the British Columbia Cancer Agency

Ovarian Cancer

- Germ Cell:
  - Dysgerminoma
  - Endodermal sinus
  - Teratoma etc.
- Sex cord stromal
  - Granulosa cell
    - FOX L2
  - Sertoli leydig etc
- Stromal tumors
  - Lymphoma
  - Sarcoma etc.
- Epithelial Tumors
  - Serous
  - Mucinous
  - Endometriod
  - Clear cell etc.

Objectives

- To discuss why epithelial ovarian cancer is becoming vanishingly rare!
- To discuss our new insights into ovarian cancer
  - **Epithelial Ovarian Cancer** is a least five distinct diseases
    - High Grade Serous*
    - Endometriod*
    - Clear cell*
    - Mucinous
    - Low Grade Serous
    - (and possibly transitional cell)
- To discuss the clinical implications of the changes in our understanding of the origin of "Ovarian Cancers"

"Ovarian" Cancer in Canada

- modest lifetime risk of 1/70, **but**:
  - major public health issue:
  - 2500 new cases/annum: 1750 deaths

- potential years of life lost from cancer:

• breast	94,400 =	**1.0**
• ovary	28,600	**0.3**
• uterus	11,400	
• cervix	10,100	

International Benchmarking

- The Lancet, Volume 377, Issue 9760, Pages 127 - 138, 8 January 2011

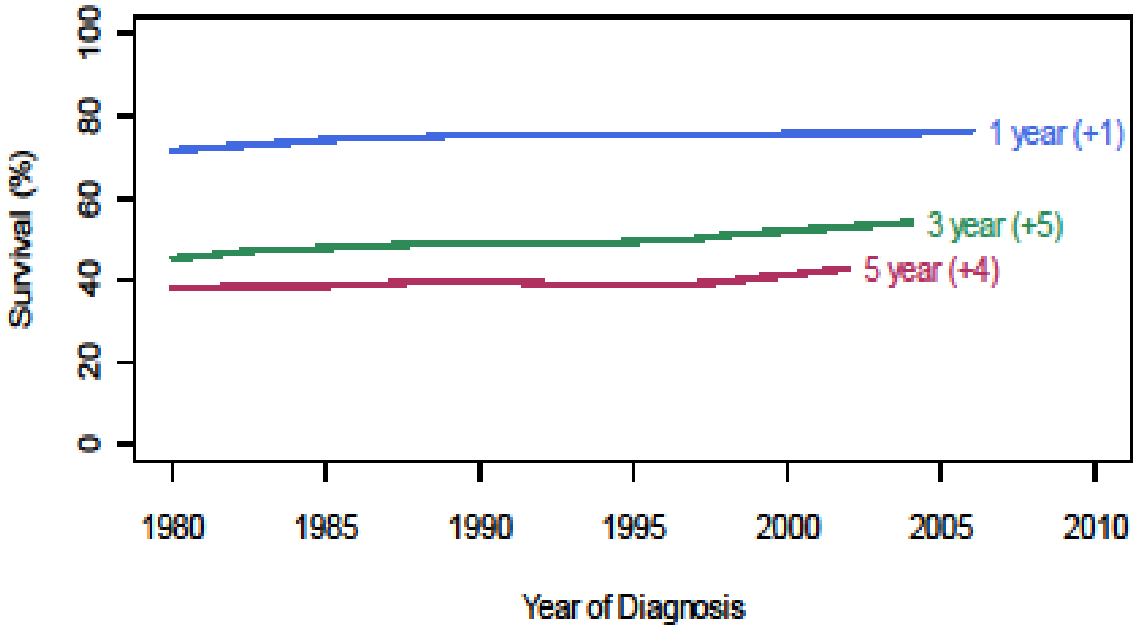
- Published Online: 22 December 2010

- **Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995—2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data**

“Ovarian Cancer”

- Screening ineffective
- Survival rates low & stable

Ovary



"Ovarian Cancer" Presentation

- 1/3 gradual intrapelvic growth →
  - lower GI & bladder Sx
  - self-identified mass
  - often low stage:
    - Clear cell
    - Endometrioid
    - Mucinous histology
- 2/3 early transperitoneal spread →
  - GI dysfunction, early satiety, ascites
  - often high stage,
    - high grade serous histology

Ovarian Cancer

- Until recently: all were thought to have the same cell of origin: the OSE or (ovarian surface epithelium)
- Now at least 5 distinct diseases

Endometroid and Clear Cell: Ovarian Cancer?

- 25% of epithelial cancers
- Universally associated with endometriosis
- Cancers of endometriosis
- Dependant on unique mutations
  - ARID 1A*
- Tend to be younger
- More likely to be localized to the pelvis
- Less likely to respond to chemotherapy (clear cell)
- More radiotherapy sensitive
- Endometroid may be hormone sensitive and behave similar to uterine cancer

Weigand, Huntsman et al NEJM Sept 2010

Endometroid and Clear Cell Cancer

- New Questions:
  - Why do the cancers form much more commonly in ovarian endometriosis (in endometriomas) than in ectopic endometriosis?
    - Hormonal milieu?
    - Other stromal factors?
  - Is there an identifiable pre-cursor lesion?
    - Atypical endometriosis (Arid 1-A mutations, high proliferation index etc.)
  - What is the risk of developing cancer with endometriosis? With endometriomas?

Endometroid and Clear Cell

- Frequency of endometriosis:
  - 12-20% of women
- Frequency of endometriomas
  - 3-5%
- Endometrioma may represent a significant risk factor

25% of ovarian cancers are endometroid or clear cell: Develop in the 3-5%of women with endometriomas

Which Endometriomas should we worry about?

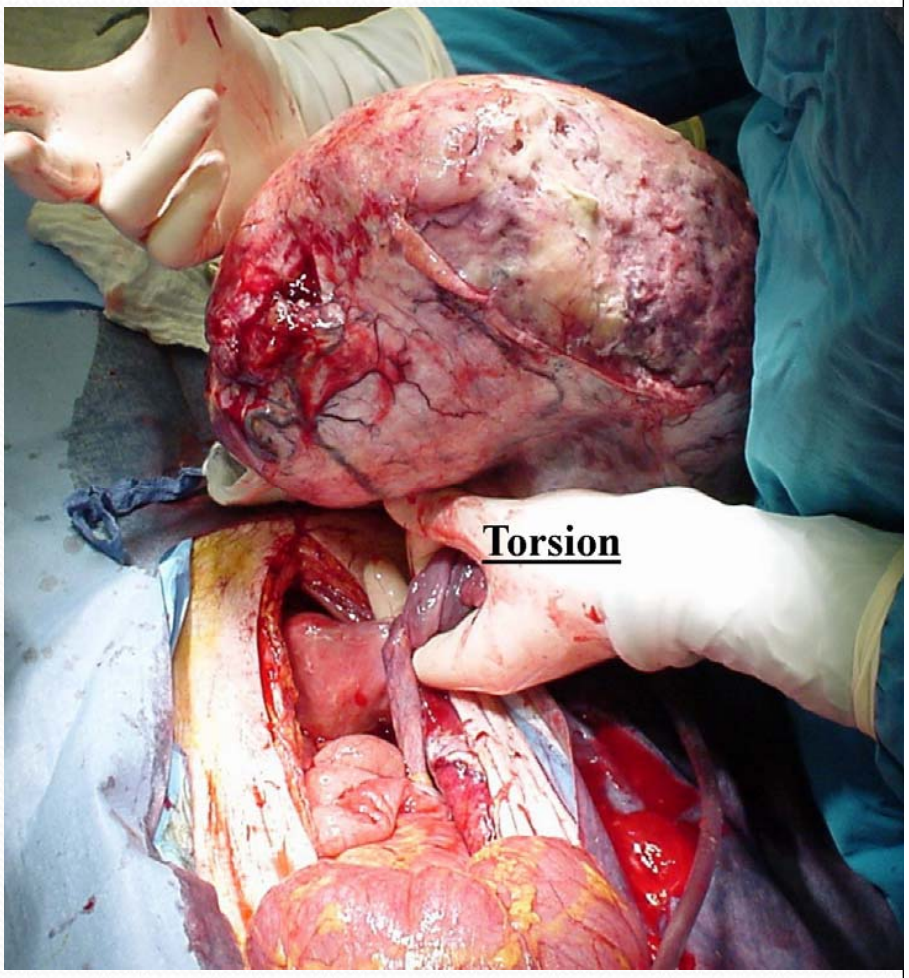
- Those with complexity
  - Irregular internal surface
    - Septae
    - Internal excresances
- Any that increase in size post menopausally

Low Grade Serous

- Indolent and rare
- Not particularly chemo sensitive
- Can develop from LMP tumors
- Psammoma bodies abundant, may be intensely calcified
- May be hormone responsive
- NOT related to the high grade serous cancers
  - not associated with p53 mutations
- May be true cancers of the ovary?

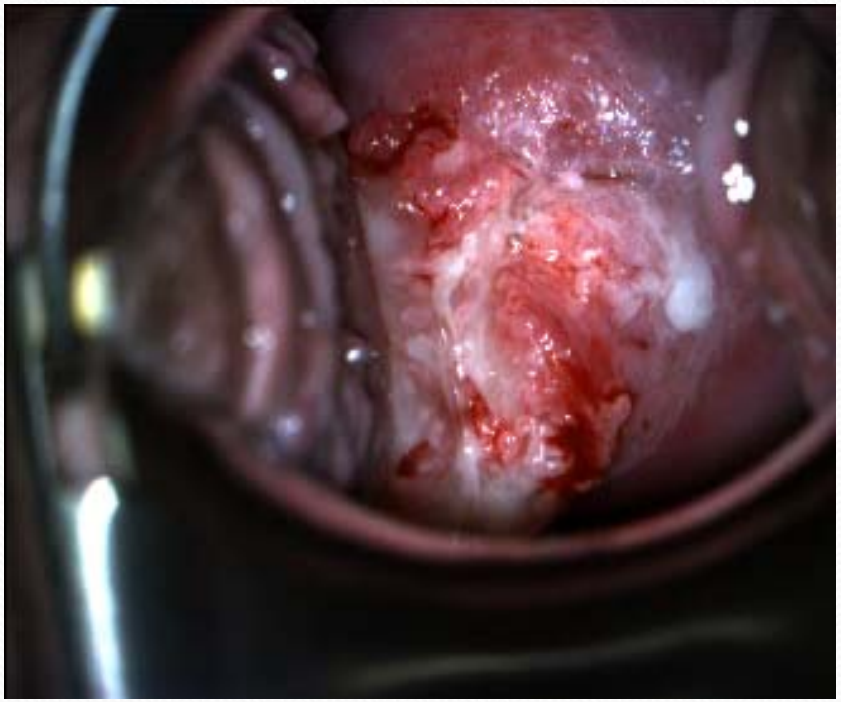
Mucinous tumors

- Malignant tumours very rare (approx 2-4%)
- Benign and borderline common
- Poor response to traditional chemotherapy
- Significant proportion (up to 1/3) over express HER 2
  - Potential for targeted treatment*
- Optimal treatment??



McAlpine et.al BMC Cancer 2009

Mucinous tumors: Ovarian Cancer?



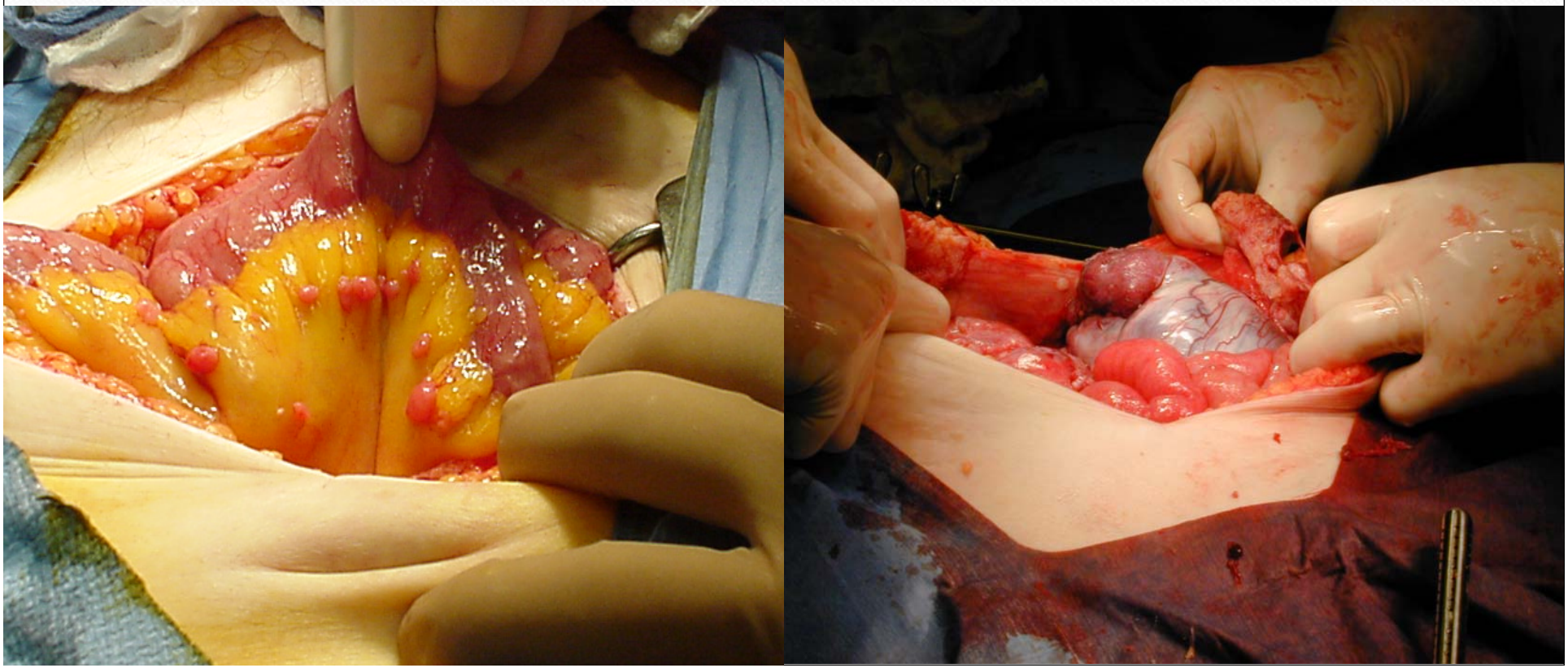
HPV Positive Tumors?

- At least some Mucinous tumors are associated with Cervical lesions
  - AIS
  - Early invasive adenocarcinomas of the cervix
- HPV and p16 positive

Elishaev E, Gilks CB et Al Am J Path 29:3 2005

High Grade Serous: Ovarian Cancer?

- Pelvic High grade Serous Tumors



Serous Tumors: objectives

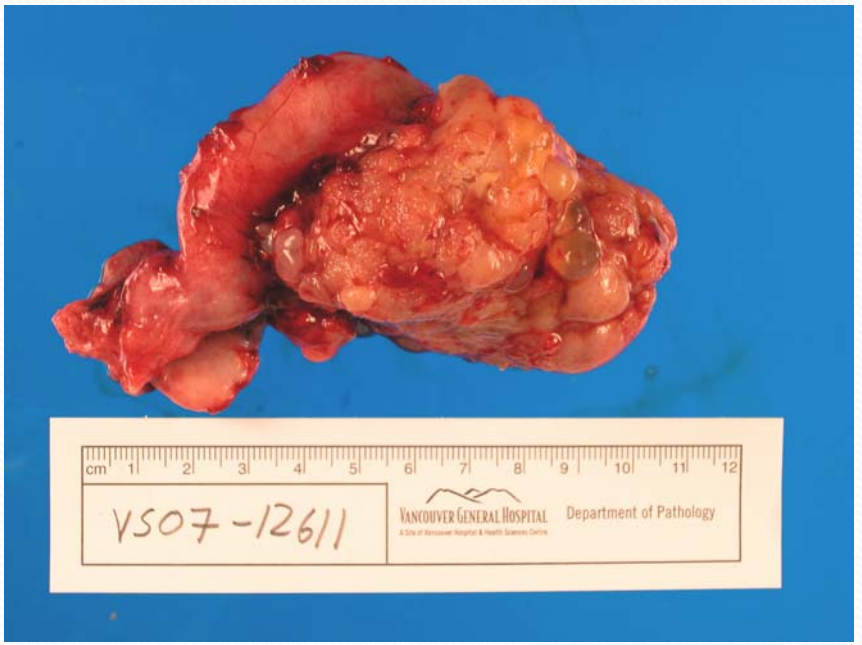
- Discuss the evidence for a tubal origin
- Understand the clinical implications of a proposed tubal origin for most Pelvic serous cancers
- Discuss the potential impact of alterations in surgical practice on the incidence and mortality from ovarian Cancer.
- Discuss the acceptability of change amongst practicing gynecologists

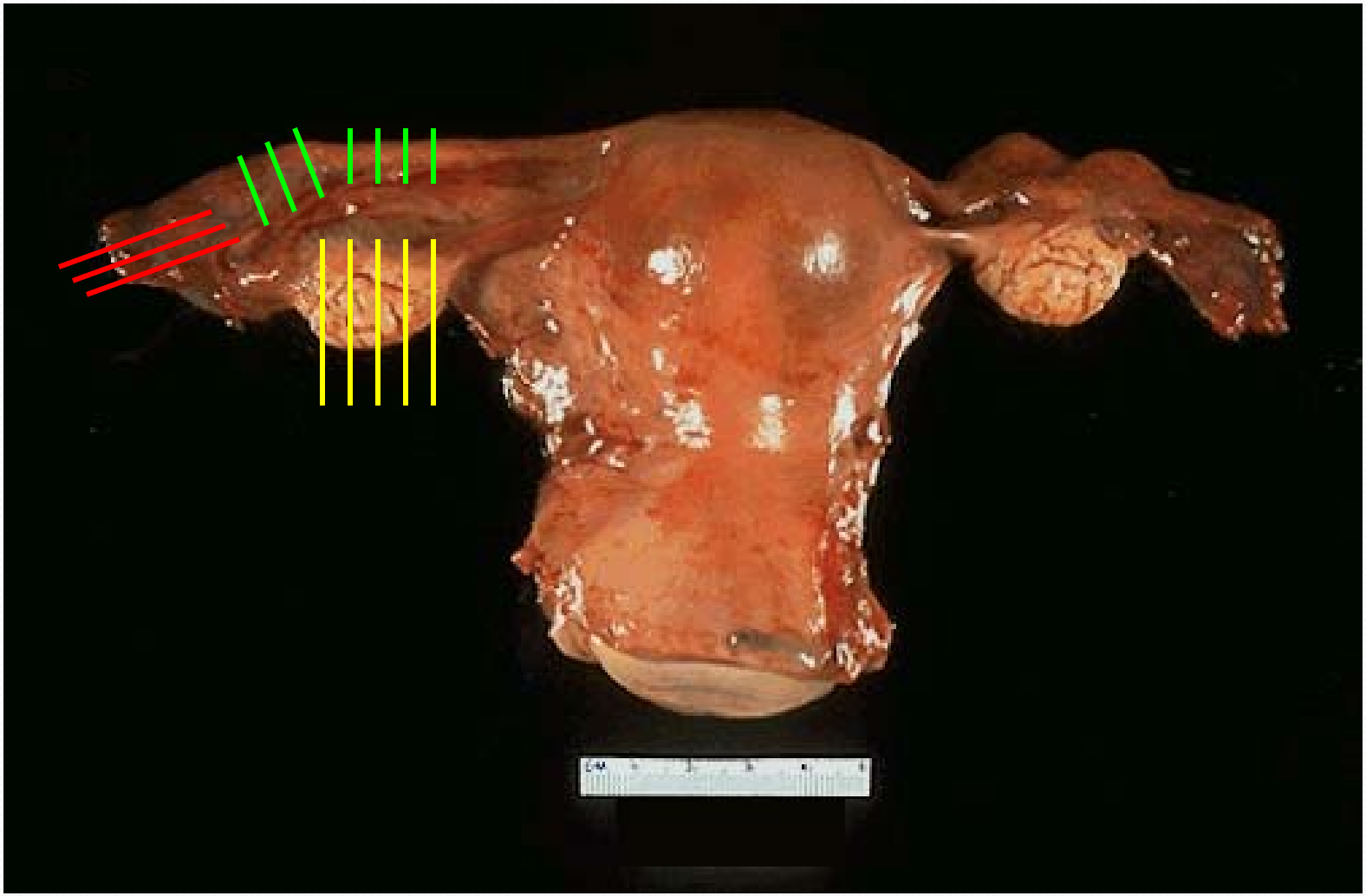
Is there a precursor lesion to "ovarian carcinoma"?

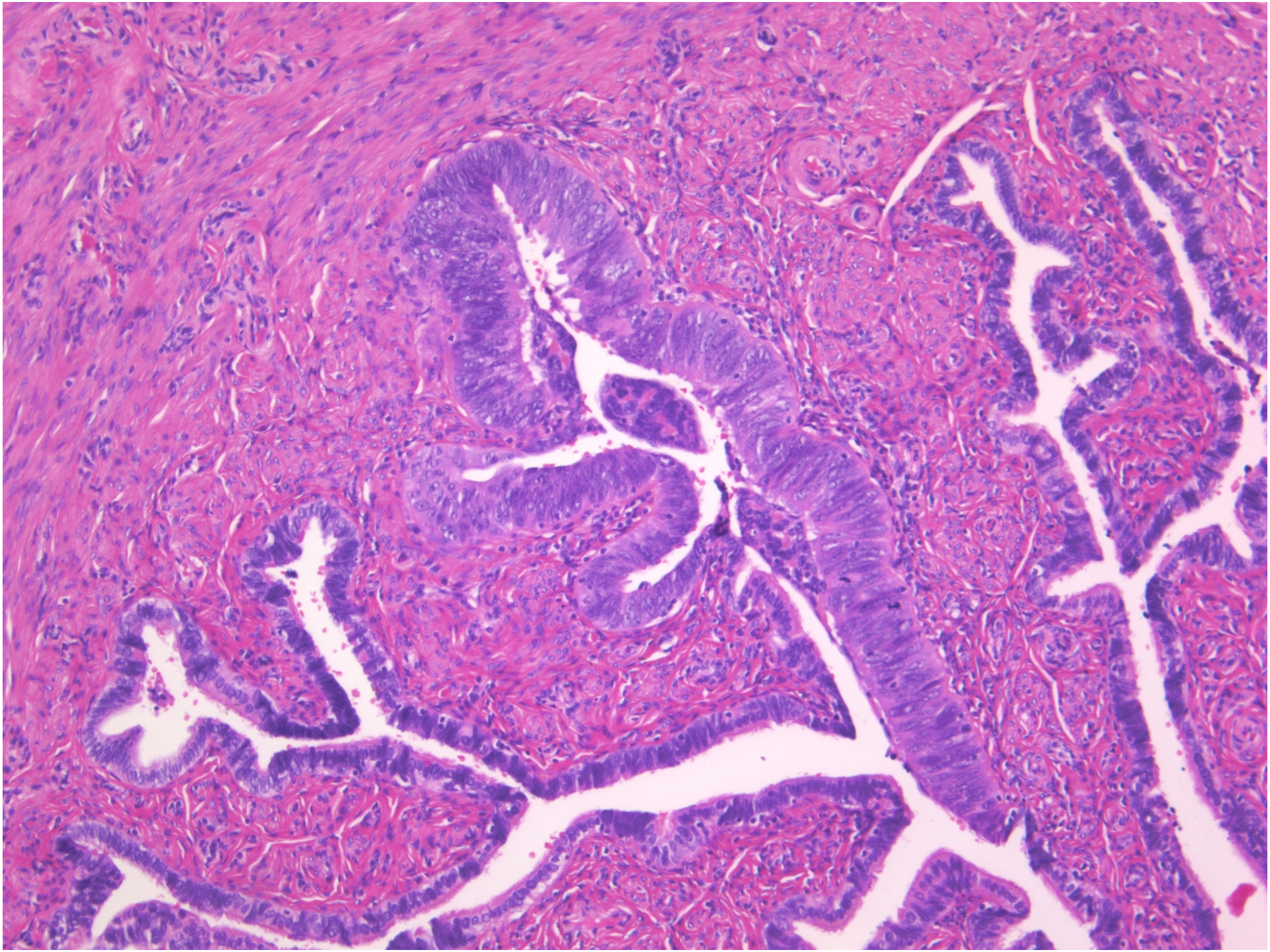
- Cervix (CIN), colon (adenoma) and breast (ductal in situ) all have precursor lesions
- What about ovarian cancer?
- 10 years ago….no precursor or in situ lesion was known

The Lesson from BRCA

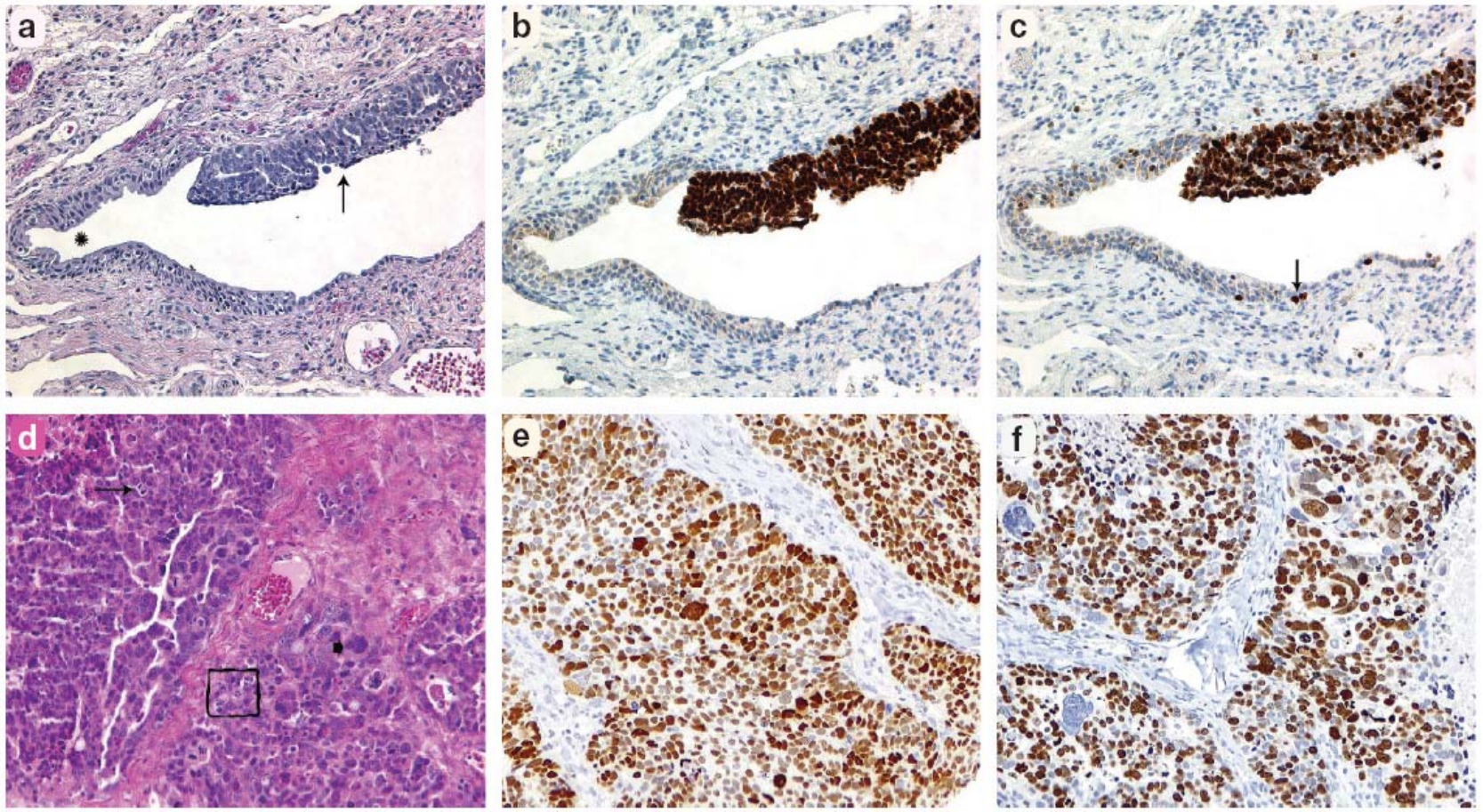
- Precursor lesions identified in prophylactic BSO specimens from BRCA mutation carriers
- Early studies had found nothing
- BUT when fallopian tubes scrutinized more carefully – more in situ cancers found







Tubal intraepithelial carcinoma



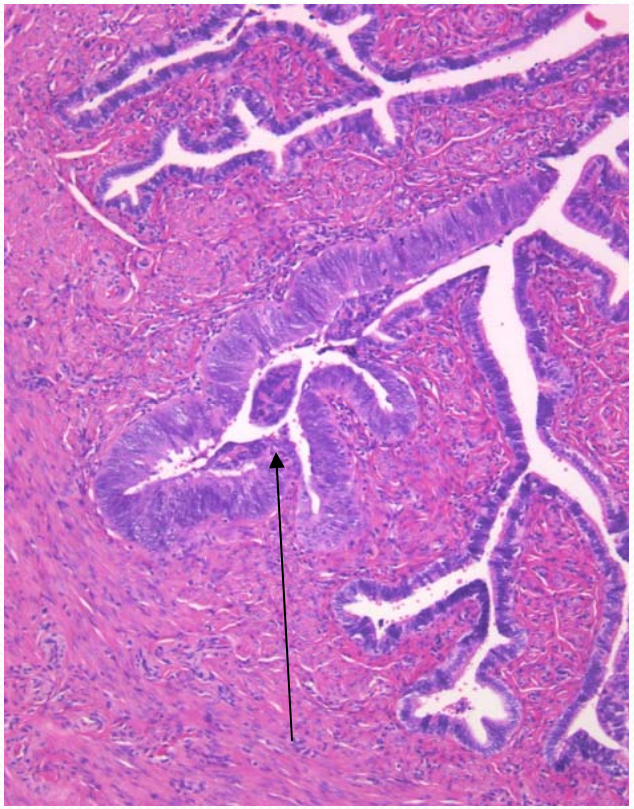
Köbel et al. Expert Rev Mol Med. 2008 Aug 1;10:e22

Implication: There is a precursor!

- Most pelvic serous carcinoma (ovary, tubal, primary peritoneal) **ARISE FROM THE FIMBRIATED END OF THE FALLOPIAN TUBE**
- Pelvic serous carcinoma accounts for 90% of advanced staged "ovarian cancer"

The Evidence

- In 75% of cases of 'advanced ovarian cancer'*
  - Data from our center on successive cases**
- Intraepithelial mucosal involvement, or total destruction of the tube ipsilateral to the largest ovarian mass.
- Unilateral fallopian tube mucosal involvement**



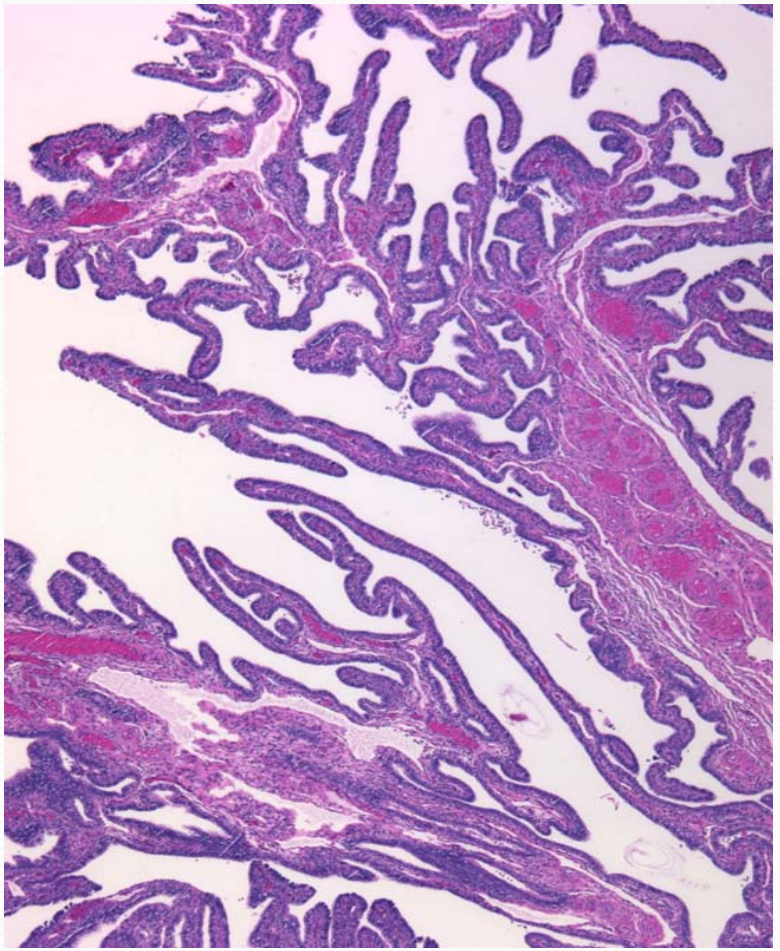
Intraepithelial cancer

*Kindelberger et al. AmJ Surg Path Feb 07
**Salvador: Gyn Onc 2008

The Fallopian Tube Makes Sense!

The native histology of the fallopian tube epithelium is mullerian serous

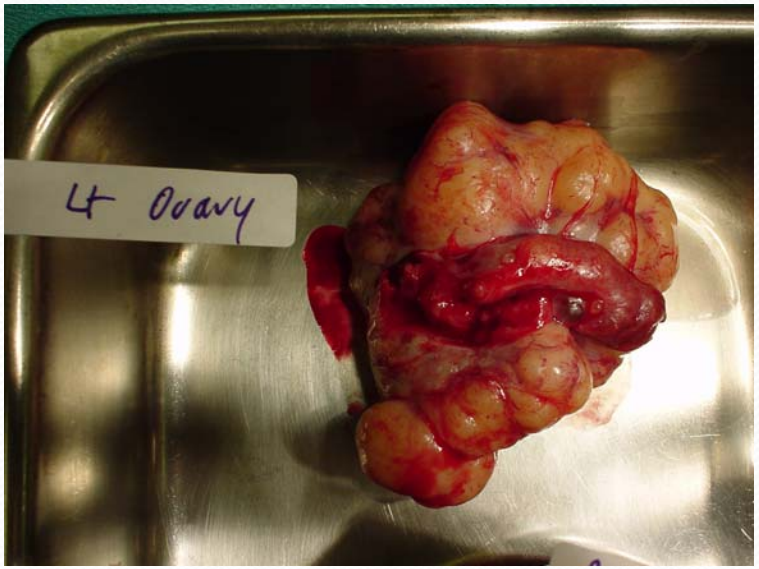
- For the ovarian epithelium(OSE) to be the source of these cancers there would have to be:
  - transformation to a mullerian type epithelium
  - malignant transformation or invagination of tubal epithelium on the surface of the ovary
- The surface area of the fimbriated end of the tube is huge compared with the surface area of the ovary



Possible Inflammatory Etiology

•Inflammation/infection is the trigger for many cancers

- Ascending infection
- Pelvic inflammatory disease(PID) is linked to ovarian cancer*
- Tubal factor infertility(OR 3.24)** and infertility related to endometriosis(OR 2.48) is associated with a higher risk of ovarian cancer
- Oral Contraceptive Pill use, Pregnancy and tubal ligation all decrease the incidence of PID and the risk of Serous Ovarian Cancer



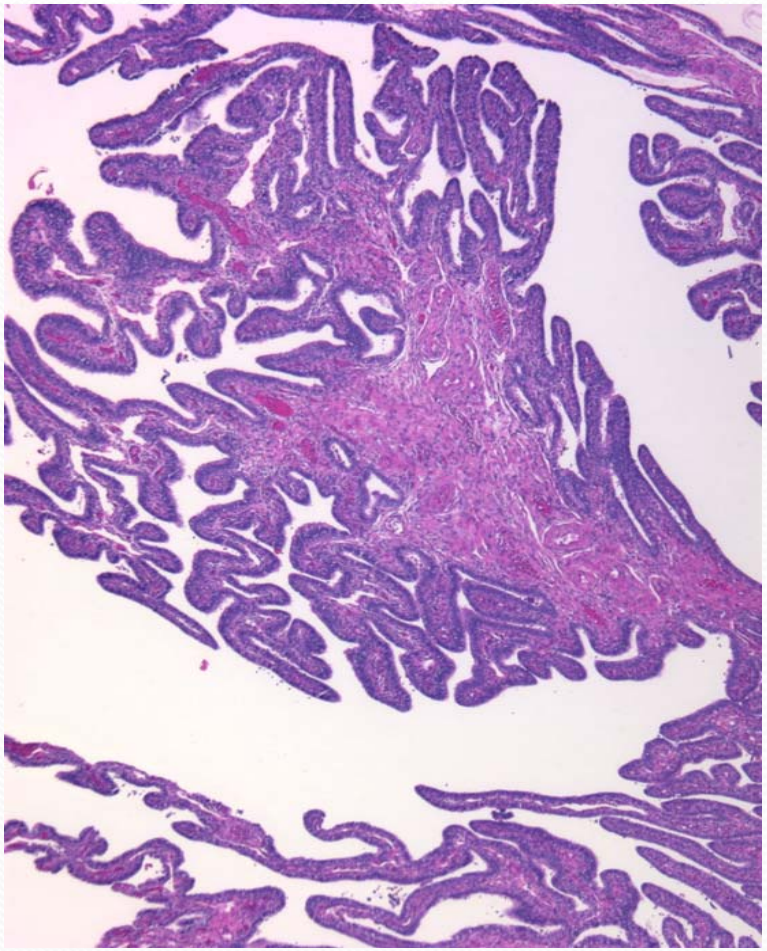
*Risch et al Ca Epi, Biomarkers and Prevention July 1995
**Brinton et al: Fertility and Sterility, Aug 2004
***Ness et al: JNCI, Sept 1999

Ascending Inflammation/Infection

There is known retrograde flow of menstrual blood at the time of menses

- Menstrual blood is found in the pelvis at menses laproscopically
- Menstrual blood is rich in inflammatory cytokines
  - IL2, IL 8, IL 12, Il 1a,TNFa, GM-CSF, etc. etc*

*Strandall et al: J Assist Repro& Genetics, July 2004



Subtype-specific odds ratios for invasive epithelial ovarian cancer associated with tubal ligation

Histological subtype	Cases (n=7451)	Adjusted* OR (95% CI)
Serous	4772 (64.0)	0.81 (0.74-0.88)
High Grade	4444	0.81 (0.74-0.89)
Low Grade	328	0.83 (0.60-1.16)
Endometrioid	1317 (17.7)	0.62 (0.48-0.80)
Clear Cell	754 (10.1)	0.48 (0.40-0.58)
Mucinous	608 (8.2)	0.52 (0.41-0.67)

* Conditional logistic regression stratified by site and age (5-year groups) and adjusted for age (continuous), race/ethnicity, OC use, and parity.

Abstract 2011 GOC S. Salvador et. al.

Early Stage High Grade Serous Tumors are Very Rare

PCT * RFS_censore Crosstabulation

			RFS_censore		
			event	censored	Total
PCT	EC	Count	1	45	46
		% within PCT	2,2%	97,8%	100,0%
		% of Total	,8%	38,1%	39,0%
	MC	Count	1	19	20
		% within PCT	5,0%	95,0%	100,0%
		% of Total	,8%	16,1%	16,9%
	CC	Count	4	24	28
		% within PCT	14,3%	85,7%	100,0%
		% of Total	3,4%	20,3%	23,7%
	HG-SC	Count	7	12	19
		% within PCT	36,8%	63,2%	100,0%
		% of Total	5,9%	10,2%	16,1%
	LG-SC	Count	0	3	3
		% within PCT	,0%	100,0%	100,0%
		% of Total	,0%	2,5%	2,5%
	TCC	Count	0	1	1
		% within PCT	,0%	100,0%	100,0%
		% of Total	,0%	,8%	,8%
	Squamous	Count	0	1	1
		% within PCT	,0%	100,0%	100,0%
		% of Total	,0%	,8%	,8%
Total		Count	13	105	118
		% within PCT	11,0%	89,0%	100,0%
		% of Total	11,0%	89,0%	100,0%

Figo stage IA and IB

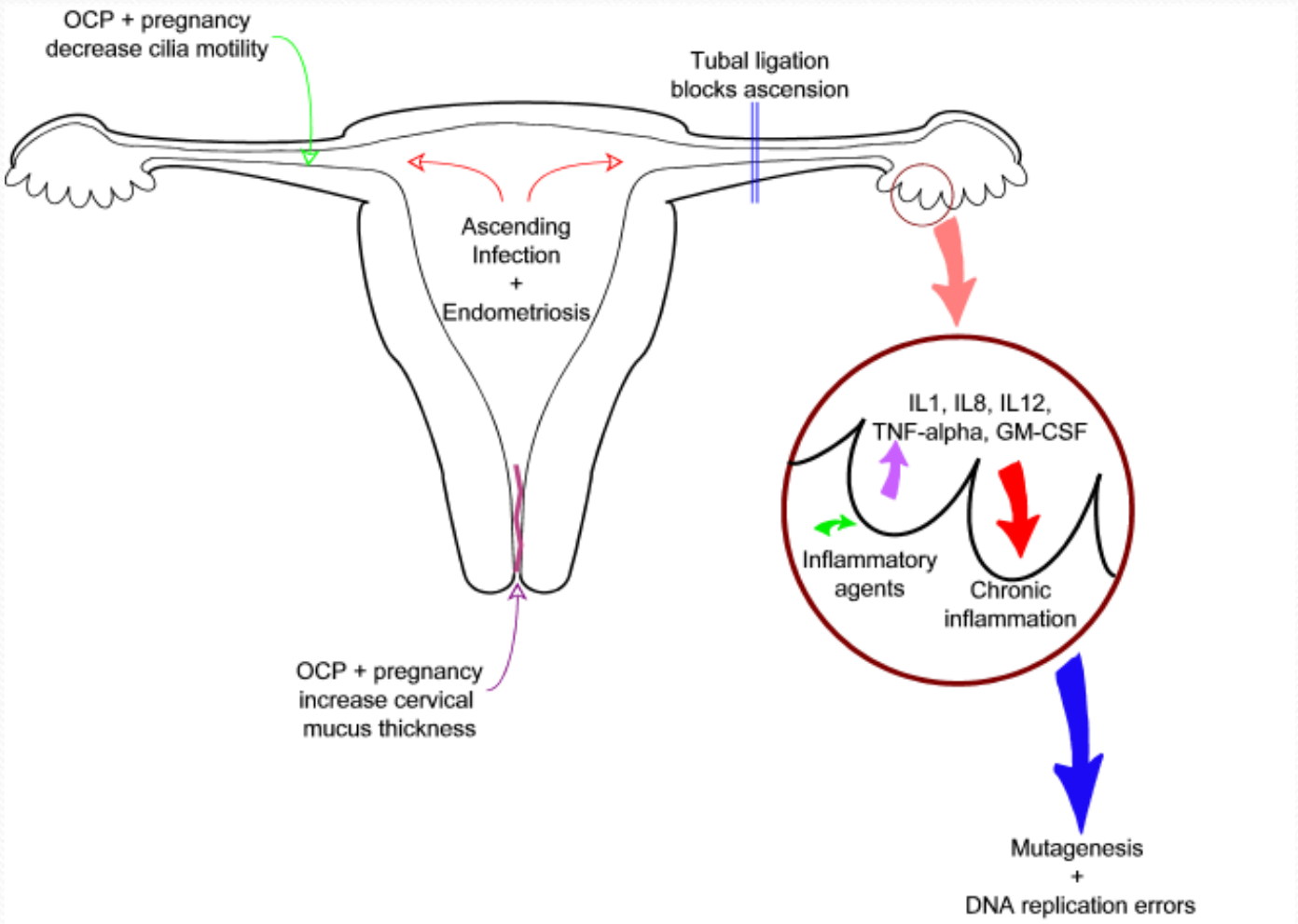
recurrences in the high-grade serous
ategory on follow up:

Progressionsite

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	12	63,2	63,2	63,2
	pelvis only	2	10,5	10,5	73,7
	pelvis and abd	3	15,8	15,8	89,5
	extra abd/pelvis lympha	2	10,5	10,5	100,0
	Total	19	100,0	100,0	

*Cheryl Brown outcomes Unit: Martin Koebel

Proposed Pathogenesis of Fallopian Tube Cancer



The Lesson from BRCA

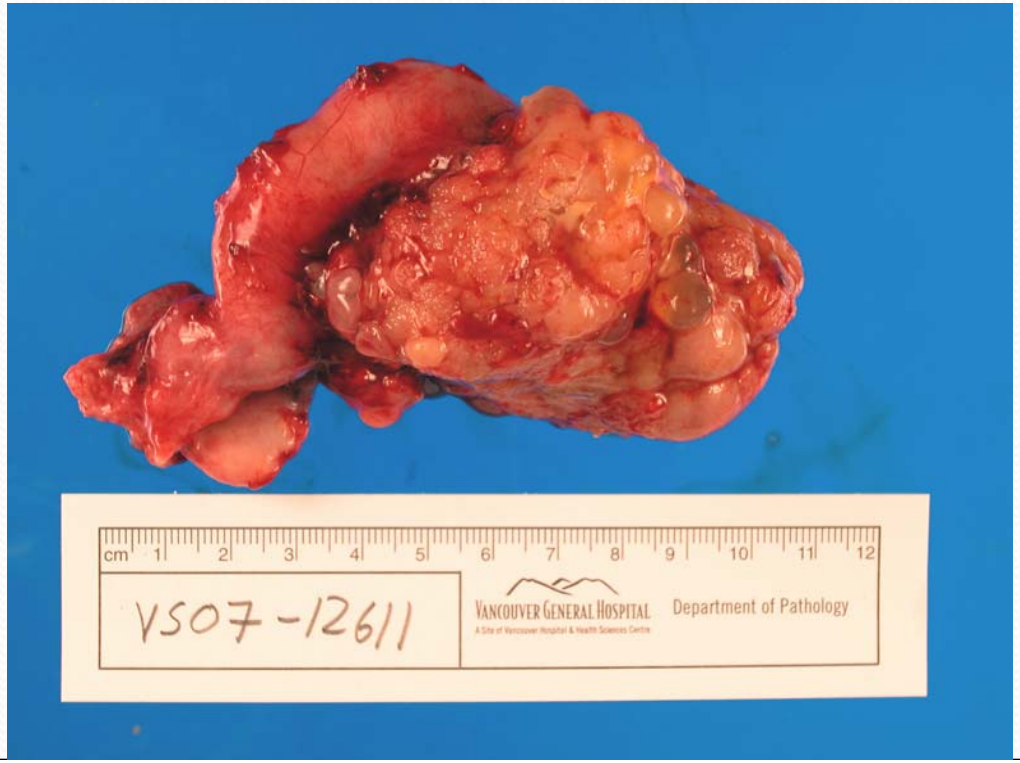
- In hereditary “ovarian cancer” the PRECURSOR is in the FALLOPIAN TUBE (tubal intraepithelial carcinoma)
- The same holds true for sporadic serous cancers

Why is this important?

- Prevention:
  - In Canada almost 50 thousand women have hysterectomies per year
  - 2/3 have the ovaries and fimbriated end of the tube left in situ
  - 18% of patients in the Ovarian Cancer outcomes data base had a hysterectomy prior to their diagnosis
  - A further 30% of patients under go tubal ligation

Prevention: removing the precursor

- Fallopian tube in situ lesions are precursor to "ovarian cancer"



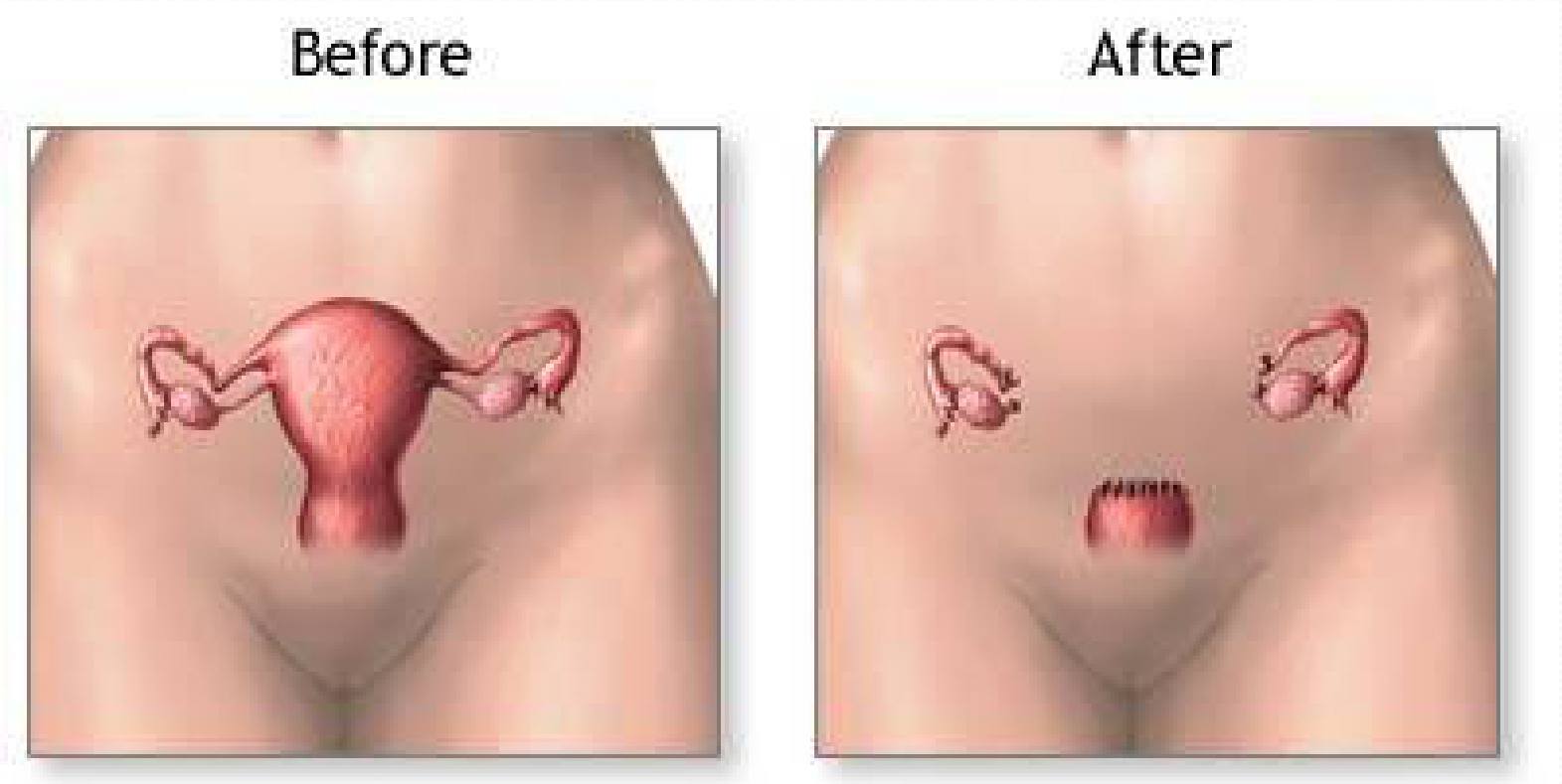
Projected Outcome

- **Conservatively in North America, up to 50% reduction in ovarian cancer deaths after 20 years**
  - **Up to 20% through salpingectomy at time of hysterectomy**
  - **Up to 20% through salpingectomy instead of tubal ligation**
  - **Up to 20% through risk-reducing BSO in patients with BRCA mutations**

Clinical Implications

- We should change how hysterectomy is done with removal of the entire fallopian tube
  - Potential to prevent 20% of cancers
- We should consider fimbrectomy for tubal sterilization
  - Potential to prevent further 15-20 % of cancers

Fimbriated ends of Fallopian Tubes are left in situ along with the Ovaries at Hysterectomy



Will Surgeons Change

- September 2010:
- British Columbia Ovarian Cancer Prevention Project
  - Encourage Oophorectomy
    - Press release and the launch of an educational campaign
    - National media coverage
    - Distribution of learning materials to all practicing gynecologists in British Columbia (available on Web)
  - Encourage referral of all HGS cancer patients for BRCA testing (over 1/5 will test positive)

www.ovcare.ca

And what about the Pathology

- How should these low risk tubes be processed?
- 685 cases: tubes serially sectioned
  - 123 single tube
  - 562 both tubes
  - 660 cases had no risk factors
    - 53 tics found: all in cases of patients with high grade serous cancer or with known BRCA mutation

Processing the tube

- Representative sections of the fimbriated end only in low risk women is appropriate

Conclusion

- Simple changes in surgical practice may have the potential to have a significant impact on the incidence and mortality from high grade serous pelvic cancer.
- Minimal to no increase in resources or surgical morbidity
- Knowledge translation and ongoing population follow up is important

The world is watching!

Wide spread interest

-NCI

- Sweden

-Northern California,

-Texas,

-Ireland

-Saudi Arabia

-UK

-Germany

Etc. etc.

Future considerations:

- Potential for the development of a screen?
- Novel imaging technologies
- Fallopian tube is accessible via the lower genital tract
  - Secretions with unique protein signatures, micro RNA etc…
  - Host responses to tumor proteins
  - Cytology?

Ovarian cancer is becoming rare!

- Serous tumors originate in fallopian tube
- Endometroid and clear cell are cancers of endometriosis
- Some mucinous tumors are HPV related

Summary

- Change in understanding of the origin and natural history of epithelial ovarian cancers
- Implications for
  - Prevention
  - Screening and treatment
- Thank you

Acknowledgements:

- OvCare British Columbia
  - David Huntsman: The UBC Chew Professor
  - Blake Gilks
- Division of Gynecologic Oncology at UBC
  - All our fellows and residents
- Ovarian Cancer Canada