Ovarian Cancer: The New Paradigm
(and what you need to know clinically)

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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
  - Endometrioid
  - 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 at 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


- 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
“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

TP53

Ki67

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**

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

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Cases (n=7451)</th>
<th>Adjusted* OR (95% CI)</th>
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<td>4772 (64.0)</td>
<td>0.81 (0.74-0.88)</td>
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<tr>
<td>High Grade</td>
<td>4444</td>
<td>0.81 (0.74-0.89)</td>
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<td>Low Grade</td>
<td>328</td>
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<td>Endometrioid</td>
<td>1317 (17.7)</td>
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<td>Clear Cell</td>
<td>754 (10.1)</td>
<td>0.48 (0.40-0.58)</td>
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<tr>
<td>Mucinous</td>
<td>608 (8.2)</td>
<td>0.52 (0.41-0.67)</td>
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* Conditional logistic regression stratified by site and age (5-year groups) and adjusted for age (continuous), race/ethnicity, OC use, and parity.
Early Stage High Grade Serous Tumors are Very Rare

**PCT * RFS_censore Crosstabulation**

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<td>% of Total</td>
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**Progressionsite**

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</table>

*Cheryl Brown outcomes Unit: Martin Koebel
Proposed Pathogenesis of Fallopian Tube Cancer

OCP + pregnancy decrease cilia motility

Tubal ligation blocks ascension

Ascending Infection + Endometriosis

OCP + pregnancy increase cervical mucus thickness

IL1, IL8, IL12, TNF-alpha, GM-CSF

Inflammatory agents

Chronic inflammation

Mutagenesis + DNA replication errors
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 undergo 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