Learning Objectives

- Understand risk factors for hereditary cancer
- Define risks related to BSO in young women
- Adopt family history screening in practice
- Review results of Nurses Health Study
- Assess impact of personal and family history of cancer
- Learn management options for BRCA patients
- Learn management options for Lynch patients
- Consider role of risk reduction strategies

Pelvic Serous Cancer (PSC)

- Ovary Cancer
- Fallopian Tube Cancer
- Primary Peritoneal Cancer
Hereditary Cancer?

- Multiple cases within the family
- Autosomal dominant transmission
- Early age of onset; earlier in successive generations
- Bilateral cancers
- Synchronous cancers (≥ 2 at once)
- Metachronous cancers (more than one, diagnosed at different times)

Red Flags for Hereditary Cancers

- Multiple cases within the family
- Autosomal dominant transmission
- Early age of onset; earlier in successive generations
- Bilateral cancers
- Synchronous cancers (≥ 2 at once)
- Metachronous cancers (more than one, diagnosed at different times)

Obtaining a Family History of Cancer

- 3-generation family history
  - 1st Generation: Parents, siblings, children
    - 50% genetic link
  - 2nd Generation: Grandparents, grandchildren, aunts, uncles, nieces, nephews, ½ siblings
    - 25% genetic link
  - 3rd Generation: Great-grandparents, great-grandchildren, great aunts/uncles, grand nieces/nephews, first cousins
    - 12.5% genetic link
Obtaining a Family History of Cancer

- Maternal and paternal data
- Include race, ethnic background, current age, all types of cancers, age at diagnosis, age at death
- Update at each visit
- Confirm with medical records and pathology reports when possible

Patient Cancer Hx Form

Identifying Individuals at Risk

- Personal and Family History
  - The most important and cost-effective tool in risk assessment
- Risk Factors for BRCA1 and BRCA2
- Amsterdam Criteria or Bethesda Criteria for HNPCC
- Gail Model for Breast Cancer Risk
Case study
- 71 yo referred. Ascites, pelvic mass
- PMH – Breast cancer age 32
- Fam hx – Sister breast cancer age 34 alive
- Surgery Illc Fallopian tube primary (PSC)
- “You and your sister both are BRCA +”
- “I have 6 brothers and 3 sisters”
- “Send them all in”
- To date…..8 family members are BRCA +

Early History
- 1895 – Aldred Scott Warthin
  - Michigan Chair of Pathology
  - Studied pedigree of German seamstress who first developed colon cancer but ultimately died of endometrial cancer
  - Published history of Family G in 1925
    - “there is some heredity to cancer”
- 1971 – Henry Lynch
  - Studied Family G
  - 2 additional families (M and N)
  - Extended the range of malignancies to include ovary renal pelvis, stomach, small bowel, pancreatic
  - Determined autosomal dominant inheritance
  - Solidified early age of onset of cancers

Mary–Claire King
Geneticist. U Washington
- Discovered Gene for BRCA 1
The Angelina Jolie Effect:
Risk Reducing Surgery for Breast and Ovarian Cancer

MAY 2013

Old Paradigms/New Paradigms
- Remove tubes/ovaries after 40 yo
  - Prevent ovary cancer?
- Remove tubes/ovaries after 50 yo
  - Prevent ovary cancer?
- Keep normal tubes/ovaries till early 60s
  - Nurses Health Study!!
- Opportunistic salpingectomy???
Bilateral oophorectomy is associated with increased mortality in women aged younger than 50 years who never used estrogen therapy and---

at no age is oophorectomy associated with increased survival.

(General population)

Parker, et al. (Obstet Gynecol 2013)
BSO AT WHAT COST?

- WITH NO HRT
  Higher rate of premature death, cancer heart disease and neurological disease

- HRT ????
  Duration?
  Compliance?

Why leave the tube in women at average risk?

In US 30% women undergo hysterectomy, 50% have ovaries and fallopian tube left in situ

- 20% of women who develop ovarian cancer have had a prior hysterectomy
- Up to 20% of ovarian cancer patients have had a tubal ligation

Most women with inherited risk are unidentified.

Hereditary Cancers in Women

- Hereditary Breast and Ovary Syndrome
  - Genes: BRCA1, BRCA2

- Lynch Syndrome
  - Nonpolyposis colorectal cancer (HNPCC)
  - Genes: MSH2,MLH1,MSH6,PMS2,EPCAM

- Li–Fraumeni Syndrome
  - Gene: TP53

- Cowden Syndrome
  - Gene: PTEN
Hereditary Cancers in Women

- Hereditary Breast and Ovary Syndrome
  - Breast, Ovary, Pancreatic, Prostate, Melanoma, Male Breast
- Lynch Syndrome
  - Colorectal, Endometrial, Ovary, Renal pelvis, small bowel, biliary tract
- Li–Fraumeni Syndrome
  - Breast, sarcoma, leukemia, brain, adrenal
- Cowden Syndrome
  - Breast, Endometrial, thyroid

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0.2–0.3% BRCA mutation carrier rate in US population
- This means 322,000 – 483,000 US women carry mutations.

In 2014 only 26% of women with ovarian cancer were tested for BRCA Mutations among patients who meet guidelines for BRCA testing.

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Ovarian Cancer Risk Factors: 
Increased Risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Hx of Breast Cancer</td>
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<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>1st Degree Relative</td>
<td>2.1</td>
</tr>
<tr>
<td>Personal History</td>
<td>10</td>
</tr>
<tr>
<td>Hx of Ovarian Cancer</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>One 1st Degree Relative</td>
<td>3.1</td>
</tr>
<tr>
<td>≥2 1st Degree Relatives</td>
<td>4-15</td>
</tr>
<tr>
<td>Hereditary Cancer Syndrome</td>
<td>12-40</td>
</tr>
</tbody>
</table>

(SEER) National Cancer Institute 
Risk Factors for Ovarian Cancer

- General Population: 1.0
- BRCA 1 Mutation: 35-46
- BRCA 2 Mutation: 13-23
- Lynch Syndrome: 3-14
- + FHx Ov Ca/ - Gene Mut.: Uncert.
- Infertility: 2.7
- PCO: 2.5
- Endometriosis (Clear Cell, Muc, LG Serous): 2-3
- + Cigs (Muc): 2
- IUD: 1.8

http://seer.cancer.gov/
BRCA 1 and BRCA 2 Function

- Tumor suppressor genes
  - Regulate normal cell growth and proliferation
  - Counteract stimulatory effects of oncogenes
- Play a role in DNA repair
  - Interact with RAD51, a known DNA repair protein
  - “Caretaker genes”

Prevalence of BRCA

- BRCA 1 general population 1:400–1:800
- BRCA 2 lower
- Ashkanazi Jewish Descent 1:40

BRCA Risk of Ovarian Cancer

<table>
<thead>
<tr>
<th>AGE</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
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<tbody>
<tr>
<td>40</td>
<td>2.2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>50</td>
<td>8.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>60</td>
<td>22%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Chen et al, JCO 2007
BRCA Mutation Prevalence: Personal Cancer History

Breast Cancer
- Dx < 50 years: 20%
- Dx > 50 years: 7%

Ovarian Cancer: 10–20%

Both Breast and Ovarian Cancer: 90%

BRCA Mutation Prevalence: Family Cancer History

Breast Cancer
- One 1st degree relative: 3.8%
- ≥ 3 relatives: 20%
- Bilateral: 18%
- Breast + ovarian cancer: 40%

BRCA1 and BRCA2-Associated Cancers: Lifetime Risks

Breast cancer: 40%–85% (often early age at onset)
Contralateral breast cancer: 40%–60%
Ovarian cancer: 15%–40%

In men, risk of breast cancer is elevated, and some studies suggest that the risks of prostate and pancreatic cancer are also elevated.
BRCA testing in patients unaffected by cancer

- 2 relatives with breast cancer, 1 < 50 yo
- 1 relative with Pelvic Serous Cancer (PSC)
- 1 relative with breast ca and 1 with PSC
- Breast Cancer in 1 male first degree relative

OPTIONS WITH BRCA or Family History

- SURVEILLANCE
- RISK AVOIDANCE
- PROPHYLACTIC SURGERY

NCCN guidelines for BRCA mutation carriers

- Remove the tubes and ovaries when between the age of 35–40 or when completed childbearing.
- Screening with CA 125 and ultrasound q 6 months.

Early Menopause??

- Cognitive impairment
- Hot flashes
- Cardiac mortality
- Sexual dysfunction
- Osteoporosis
All guidelines recommend: Risk Reducing salpingo-oophorectomy for BRCA mutation carriers

- 90% effective in reducing ovarian cancer
- 50% reduction in breast cancer if performed before age 50
- Increase life expectancy 6.6–11.7 years for combined BSO, mastectomy.

Oophorectomy reduces Breast Cancer Risk in BRCA mutation carriers

Risk reduction if performed by age 40
- BRCA 1: 56% (OR= 0.44; 95% CI 0.29, 0.66)
- BRCA 2: 46% (OR= 0.57; 95% CI 0.28, 1.15),

Domchek JAMA, 2010
Eisen et al, J Clin Oncol, 2005

Salpingectomy in mutation carriers

- Some cancer risk reduction
- Avoid premature menopause
- Maintain option for IVF pregnancy
- Option for those unwilling to have BSO
- Pros
- Cons
- Two stages to surgery
- Delay of removing the ovaries
- May not be as effective
- No Breast cancer risk reduction
SURVEILLANCE

- BREAST CANCER
  - self examination
  - mammograms
  - MRI

- OVARIAN CANCER
  - clinical examinations
  - vaginal ultrasound
  - Ca 125 level

Follow Up Studies BRCA + Pts.

HNPCC or Lynch Syndrome

- ~7% of hereditary ovarian cancer cases
- 5% of all colorectal cancer cases
- Most common cancers: COLON and ENDOMETRIAL
- Increased incidence of other adenocarcinomas, including stomach, small bowel, and bile duct malignancies (not breast)
Lynch Syndrome

- Autosomal dominant inheritable cancer syndrome
- Formerly Known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
- Responsible for most common form of hereditary colorectal cancer AND endometrial cancer

HNPCC

- Responsible genes: Mismatch repair genes (MMR) including MLH1, MSH2, and MSH6
- Autosomal dominant
- Prevalence in the general population: 0.1% (1/400 to 1/1000)

Lynch Associated Cancers

- Colorectal
- Endometrial
- Ovarian
- Renal Pelvis
- Ureter
- Stomach
- Small bowel
- Sebaceous adenocarcinoma
- Hepatobiliary
- Pancreas
- Brain (glioma)
- Prostate?
- Breast?
- Laryngeal??
- Hematologic?
Clinical Significance
- 50–80% risk of malignancy by age 70
- 7–15% will have synchronous tumors at diagnosis
- 20–65% chance of metachronous tumors
- Significantly under-recognized

Case presentation
- 40 yo G4P4 (wife of obgyn)
- Father colon cancer at 33 yo
- Sister colon cancer
- Tested for Lynch----Positive
- Advised Risk Reduction TLH, BSO
- At surgery
  - Synchronous primary cancer (uterus and ovary)
  - Colonoscopy negative
- Currently NED after surgery/chemotherapy

Women with Lynch Syndrome:
- Colon cancer:
  - 50–80% lifetime risk
- Endometrial cancer:
  - 40–70% lifetime risk
- Ovarian cancer:
  - 10–14% lifetime risk
Endometrial Cancer in Lynch Syndrome

- Similar lifetime risk to colorectal cancer
- Survival similar to sporadic
- Endometrioid common but all cell types documented
- Similar hormonal/reproductive risk modifiers to sporadic cancer
- More often lower uterine segment

Characteristics of Lynch CRC

- Predominantly right colon
- Evolve from flat large adenoma
- Rapid progression (months rather than years)
- Higher 5 year OS than sporadic tumors

Ovarian Cancer in Lynch Syndrome

- 2–14% lifetime risk
- Pathology and survival similar to sporadic
  - More likely to be diagnosed as stage I or II
- Significantly younger age than sporadic
- BRCA larger portion of familial ov cancer
Identifying Individuals at Risk

- History based
  - Amsterdam
  - Bethesda
- Prediction models
- Tumor based
  - IHC
  - MSI
- Genetic evaluation

Targeted Surveillance?

- Transvaginal Ultrasound
  - Endometrial stripe measurement (difficult premenopausal
  - Ovarian imaging
- Annual endometrial biopsy
  - Starting at age 30–35 or five years prior to earliest diagnosed LS malignancy
- CA125
- NO surveillance in this (or any other) patient population has shown improved overall survival…..but many still recommend

Clinical Management of Women with HNPCC: Screening

- Annual ultrasound or endometrial biopsy beginning at age 25–35

- Hysterectomy and BSO when childbearing complete
  - Reduces risk of endometrial cancer
  - Reduces risk of ovarian cancer
Intervention

- Risk Reducing Surgery
  - Hysterectomy/ BSO

Prophylactic Hysterectomy and BSO

- When completed child baring
- Supracervical inappropriate
- Surgeon should be prepared for complete staging procedure
- Occult cancer not uncommon at time of “prophylactic” surgery
- Frozen/intraoperative pathologic evaluation usually indicated.
- Serial sectioning of ovaries
- TAH/BSO should be offered at time of prophylactic or therapeutic colectomy
- Estrogen replacement probably acceptable in the absence of endometriod cancer
- Primary peritoneal cancer risk still 0.5–1.5%

Elevated HNPCC Risk: Amsterdam Criteria

- 1. At least two successive generations with colorectal cancer
- 2. Diagnosis of at least one individual before age 50
- 3. Colon cancer in at least 3 relatives
- 4. Family history of other cancers including ovarian, endometrial, stomach, urinary tract, small bowel, and bile duct
When might genetic testing be considered?

- Personal or family hx of pre-menopausal breast cancer OR ovarian cancer (any age)
- 1st-degree relative with BRCA1 or 2 mutation
- Family hx of ≥ 2 cases of pre-menopausal breast cancer
- Family hx of ≥ 1 cases of ovarian cancer

Genetic Testing (con’t)

- Personal or family hx of bilateral breast cancer
- Family hx of male breast cancer
- Ashkenazi Jewish ancestry in the setting of a personal or family hx of breast or ovarian cancer

Clinical Management

- Now that you’ve got it, what do you do with it?!
  - Genetic counseling/testing
  - Screening
  - Prophylactic measures/chemoprevention
  - Consider clinical trials
References

- Parker. (Obstet Gynecol 2013)
- Kuran AW, Curr Opin Obstet Gynecol 2015
- Chen. JCO 2007.
- Domchek JAMA 2010.