Importance of Family History in Gynecologic Cancer Prevention

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Objectives

- Introduce role of genetic counselor
- Discuss cancer genetics
- Explain differences between sporadic, familial, and hereditary cancers
- Explain importance of family history
- Discuss HBOC and Lynch Syndrome
- Discuss tools for your practice
- Discuss special issues

“This is your side of the family, you realize.”
Genetic counselors are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling.
Cancer Genetic Counselors- Roles

- Determine a patient’s risk for a hereditary cancer susceptibility syndrome based on personal/family history
- Provide cancer risk assessment based on a patient’s family history
- Determine what (if any) genetic tests are appropriate for a patient
  - Discuss risks, benefits, and limitations of genetic testing
  - Coordinate and interpret genetic tests
  - Provide psychosocial counseling
Distribution of Sporadic, Familial, and Hereditary Cancer

- Sporadic Cancer: 75-85%
- Familial Cancer: 10-20%
- Hereditary Cancer: 5-10%
Chromosomes, DNA, and Genes

Adapted from Understanding Gene Testing, NIH, 1995
Disease-Associated Mutations

A mutation is a change in the normal base pair sequence.
ALL CANCER IS GENETIC

BUT

NOT ALL CANCER IS HEREDITARY
Cancer results from the accumulation of mutations in cancer predisposing genes.
Low, moderate-risk genes
Shared lifestyles, environments

High-risk genes

Distribution of Sporadic, Familial, and Hereditary Cancer

Sporadic Cancer 75-85%
Familial Cancer 10-20%
Hereditary Cancer 5-10%
Hereditary Ovarian Cancer

- 20-25% of women with a diagnosis of ovarian cancer carry a hereditary gene mutation

Hereditary Endometrial Cancer

- 5% of women with a diagnosis of uterine cancer carry a hereditary gene mutation.

- 2-3% of women with endometrial cancer have Lynch syndrome.

Importance of Identification

Why is it important to identify hereditary gynecologic cancer predisposition syndromes in families?

- High risk of cancer development
- Early-onset cancers
- Multiple organ systems may be involved
- Increased risk for second primary cancer
SPORADIC CANCER = FEW OCCURRENCES OF CANCER IN FAMILY

- Onset later in life
- Few relatives with cancer

Uterine ca at 70y
FAMILIAL CANCER = CLUSTER OF CANCER WITHIN FAMILIES

Unclear inheritance pattern:
- Chance alone
- Common environment/lifestyle factors
- Shared low, moderate-risk genes
HEREDITARY CANCER

- Multiple affected individuals in multiple generations
- Early age of onset
- Individuals with multiple primaries
- Evidence of dominant inheritance
- Specific cancer clusters
Family History Features Suggestive of a Hereditary Cancer Syndrome

- Multiple family members affected with cancer in multiple generations
- Early onset cancer (before age 50)
- Clustering of specific types of cancers
  - Breast and ovarian cancer in same family
  - Colon, uterine, and ovarian cancer in same family
- Individuals with more than one cancer
  - Breast and ovarian cancers in one person
- Rare cancers
  - Male breast cancer
- Ethnic background
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)
Hereditary Breast and Ovarian Cancer Syndrome

- BRCA1
  - Breast Cancer Gene 1

- BRCA2
  - Breast Cancer Gene 2

1/400-1/800 individuals in the general population carry a BRCA1 or BRCA2 mutation

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation.
German

- d. 30’s; unknown cause

- 70’s
- 70’s
- d. 70’s
- 80
- 78
- d. 48 ovarian ca @ 43

- No Ashkenazi Jewish ancestry
- No consanguinity

Polish

- d. 78
- 79
- 62; breast ca at 48
- d. 60’s; MI

- d. 65; Bladder ca; smoker

- 46; TAH-BSO

- 25
**BRCA1/2-Associated Cancers: Lifetime Risks**

- **breast cancer:** ~45%-80% (often early onset)
- **ovarian cancer:** (BRCA1: ~40%) (BRCA2: ~20%)
- **male breast cancer:** (3-12%)

Risk is increased for other cancers including: pancreatic, prostate, melanoma

Ovarian Cancer Risk Management Options

- **Screening**
  - Concurrent transvaginal ultrasound and CA-125 every 6 months starting at age 30y or 5-10y earlier than first diagnosis of ovarian cancer in family
  - Data suggests that screening is NOT effective for the early detection of ovarian tumors

J Med Genet 2009;46:593-597
Ovarian Cancer Risk Management Options

- **Risk Reduction - Surgery**
  - Bilateral salpingo-oophorectomy between ages 35y and 40y, or upon completion of childbearing, or individualized based on earliest onset of ovarian cancer in family

- 80-95% reduction in ovarian cancer risk in BRCA1/2 positive women following RRSO

NCCN Guidelines Version 1.2013 Hereditary Breast and/or Ovarian Cancer Syndrome
Ovarian Cancer Risk Management Options

- Risk Reduction - Chemoprevention
  - Consider oral contraceptive use
  - 50% reduction in ovarian cancer risk for BRCA1/2 positive women using oral contraceptives
    - Risk appears to decrease with longer period of use
    - Conflicting data regarding OCP use and breast cancer risk for BRCA carriers

Breast Cancer Risk Management Options

- **Screening**
  - Monthly BSE beginning at age 18y
  - Semi annual clinical breast exam beginning at age 25y
  - Annual mammogram and breast MRI beginning at age 25, or individualized based on earliest breast cancer onset in family

- **Surgery**
  - Discuss option of bilateral prophylactic mastectomy

- **Chemoprevention**
  - Tamoxifen/Raloxifene
Genetic Evaluation Guidelines

- Personal and/or family history:
  - Premenopausal breast cancer (<50y)
  - Triple negative breast cancer <60y
  - Bilateral breast cancer
  - Ovarian cancer
  - Male breast cancer
  - Postmenopausal breast cancer with additional relatives with breast cancer (especially if young age of onset)
  - Known hereditary cancer susceptibility syndrome

Adapted from: NCCN Guidelines Version 1.2013 Hereditary Breast and/or Ovarian Cancer Syndrome
Lynch Syndrome

(HNPCC)
Lynch syndrome

- MLH1
- MSH2
- MSH6
- PMS2
- EPCAM (TACSTD1)
Features of Lynch Syndrome

- Early but variable age at CRC diagnosis (~45 years)
- Typically right-sided tumors
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors
<table>
<thead>
<tr>
<th>Age</th>
<th>Cause of Death</th>
<th>Smoking Status</th>
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</thead>
<tbody>
<tr>
<td>74</td>
<td>Lung cancer @ 73</td>
<td>Yes</td>
</tr>
<tr>
<td>69</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Colon cancer @ 42</td>
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<tr>
<td>48</td>
<td>MI</td>
<td></td>
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<tr>
<td>68</td>
<td>Colon cancer @ 56</td>
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<tr>
<td>72</td>
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<td></td>
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<tr>
<td>68</td>
<td>Colon cancer @ 42, Uterine cancer @ 56</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Lung cancer @ 64 (smoker)</td>
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<td>72</td>
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<td>Cancer</td>
<td>General Population Risk</td>
<td>HNPCC</td>
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<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
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<tr>
<td>Ovary</td>
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<td>9%-12%</td>
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<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2%-7%</td>
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<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
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<td>Small bowel</td>
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<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
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Uterine/Ovarian Cancer Risk Management Options

- **Screening**
  - Annual office endometrial sampling is an option
  - Transvaginal ultrasound, CA-125

- There is no clear evidence to support screening for endometrial cancer in Lynch syndrome

- No evidence to support routine ovarian cancer screening
Uterine/Ovarian Cancer Risk Management Options

- **Risk Reduction- Surgery**
  - Prophylactic TAH-BSO should be considered after childbearing is complete

- **Risk Reduction- Chemoprevention**
  - Oral contraceptives reduce risk for endometrial and ovarian cancer in the general population, although efficacy in women with Lynch syndrome has not yet been determined

Management - Men and Women

- Colon cancer
  - Colonoscopy at age 20-25y or 2-5y prior to earliest CRC diagnosis in family, repeat every 1-2y

- Gastric and small bowel cancer
  - Consider EGD, with extended duodenoscopy and polypectomy at 2-3y intervals beginning at age 30-35
  - Consider capsule endoscopy for small bowel cancer at 2-3y intervals beginning at age 30-35

- Urothelial cancer
  - Consider annual urinalysis beginning at age 25-30y

- Pancreatic cancer
  - Limited data, no current guideline
  - High-risk programs: consider annual endoscopic ultrasound and MRI

NCCN Colorectal Cancer Screening Version 2.2012
Case Examples
Case 1

- Colon ca @ 41, Uterine ca @ 56
- Lung ca @ 42, (smoker)
- Colon ca @ 42, Uterine ca @ 56
- Glioblastoma Multiforme @ 46
- MI d. 65
- Stroke d. 72
- MSH2 -
- MSH2 +

Lung ca @ 73 (smoker)
Case 1

- **Patient with Lynch syndrome**
  - Increased risk for endometrial and ovarian cancer
  - Should consider prophylactic TAH-BSO

- **Patient’s sister who tested negative for the familial MSH2 mutation**
  - Average risk for Lynch-associated cancers
Case 2

Lung ca @ 73 (smoker)

Stroke

Colon ca @ 65

Colon ca @ 70

MI

MI

d. 74

69

64

d. 48

68

72

Colon ca @ 65

45

38

44

25
Case 2

- Suspicion for LS is low
- No genetic testing for family indicated at this time
- Risk for gynecologic malignancies likely not increased over the general population risk
<table>
<thead>
<tr>
<th>Immunohistochemistry (IHC)</th>
<th>MSI</th>
<th>BRAF V600E</th>
<th>MLH1 Promoter Methylation</th>
<th>Plausible Etiologies</th>
<th>Additional Testing</th>
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<td>MSS/MSI-Low</td>
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<td>N/A</td>
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<tr>
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<td>MSI-High</td>
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<td>1.) Germline mutation in any one of the known mismatch repair genes</td>
<td>1.) Consider germline testing of MLH1 and MSH2 followed by MSH6 and possibly PMS2</td>
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<td>MSI-High</td>
<td>N/A</td>
<td>N/A</td>
<td>1.) Sporadic cancer or germline mutation in any one of the known mismatch repair genes</td>
<td>1.) If IHC not done, MLH1 and MSH2 genetic testing followed by MSH6 and possibly PMS2</td>
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<tr>
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<td>N/A</td>
<td>N/A</td>
<td>Positive</td>
<td>1.) Sporadic cancer</td>
<td>1.) Consider BRAF V600E methylation studies</td>
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<td>N/A</td>
<td>Negative</td>
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<td>1.) MLH1 genetic testing</td>
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<tr>
<td>-  +  +  +  -</td>
<td>N/A</td>
<td>N/A</td>
<td>Negative</td>
<td>1.) Sporadic cancer</td>
<td>1.) None C</td>
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<tr>
<td>-  +  +  +  -</td>
<td>N/A</td>
<td>N/A</td>
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<td>1.) Rarely germline mutation MLH1 or constitutional MLH1 epimutation</td>
<td>1.) MSH2 genetic testing, if negative TACSTD1 testing</td>
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<td>N/A</td>
<td>Negative</td>
<td>1.) Germline mutation MLH1</td>
<td>1.) MSH2 genetic testing, if negative PMS2</td>
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<tr>
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<td>N/A</td>
<td>Negative</td>
<td>1.) Germline mutation PMS2</td>
<td>1.) MSH2 genetic testing</td>
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<td>N/A</td>
<td>Negative</td>
<td>1.) Germline mutation MLH1</td>
<td>1.) MSH2 genetic testing</td>
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<td>1.) Germline mutation MLH1</td>
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<td>N/A</td>
<td>Negative</td>
<td>1.) Germline mutation MLH1</td>
<td>1.) MSH6 genetic testing, if negative MSH2</td>
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</tbody>
</table>
Personal and/or family history of:
- Colorectal cancer <50y
- Endometrial cancer <50y
- Colorectal and endometrial cancer in same individual
- Ovarian cancer
Family History
A genetic answer for the ovarian and/or endometrial cancer in a family is not always available

- Undetectable mutation in known genes (BRCA1, BRCA2, MLH1, MSH2, etc.)
- Mutation(s) in unidentified gene(s)
- Affected family members not able to undergo testing
- Cancer may be due to shared lifestyle/environmental factors, shared personal risk factors
Family History

- **Ovarian Cancer**
  - Having one first-degree relative with ovarian cancer increases a women’s risk to 1.5-4% risk
  - Having two affected relatives increases a women’s risk to 7%

- **Endometrial Cancer**
  - Having one first-degree relative with endometrial cancer increases a women’s risk 2-fold

Cancer Treat Res. 2010; 156: 69-85
Family History

- Risk reducing surgery may be indicated for women with a strong family history
  - Definition for “strong family history” unclear
  - Recommendations for screening/prophylactic surgery provider-dependent
Family History- Tools For Your Practice

- Who?
  - Siblings, children, parents, aunts, uncles, grandparents, cousins
  - Maternal AND paternal relatives
  - Ancestry

- What?
  - Cancer type
  - Age of diagnosis
  - Unusual pathologic features
  - Multiple primaries
Extremely important to gather family history for each patient and to develop a process that works well for your clinic

- Paper screening forms
  - Physician or nurse directed questioning
- Family history questionnaires in the electronic medical record
- On-line tools
  - Surgeon General Family History Tool
My Family Health Portrait
A tool from the Surgeon General

Using My Family Health Portrait you can:

- Enter your family health history.
- Print your family health history to share with family or your health care worker.
- Save your family health history so you can update it over time.

Talking with your health care worker about your family health history can help you stay healthy!

Learn more about My Family Health Portrait

Create a Family Health History

En Español

Use a Saved History

Em Português

In Italiano
Family History-Tools For Your Practice

- ***Family history changes over time***

- Important to consider how a patient’s family history will be updated and stored in your clinic
Special Issues
Insurance

- Genetic testing is expensive
- Varying coverage for genetic services from one insurance company to another
  - Most insurance companies cover genetic testing when medically necessary
- Some plans have direct exclusions to genetic testing
- Genetic counselors can help!
Genetic Discrimination - GINA

- Genetic Information Nondiscrimination Act of 2008 (GINA)
  - Health insurance
    - Prohibits use of genetic information in setting eligibility or premium or contribution amounts by group and individual health insurers
    - Prohibits health insurers from requesting or requiring an individual to take a genetic test
  - Employment
    - Prohibits use of genetic information by employers in making decisions regarding hiring, firing, and promoting
    - Prohibits employers from requesting, requiring, or purchasing genetic information about an individual employee or family member
Questions?
References


References