Lynch Syndrome for the Gynecologist

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Disclosures

• None
Outline

- History
- Cancer Risks
- Etiology
- Diagnosis
- Screening
- Prevention
History
History of Lynch Syndrome

- 1913: Aldred Warthin
  - Family G
- 1966: Henry Lynch
  - 2 additional families
  - Early age onset
  - Autosomal Dominant
- 1984: “Lynch Syndrome”
- 1985: “HNPCC”
- 1991: Amsterdam Criteria
  - 1999: Amsterdam II Criteria
- 1998: Bethesda Guidelines
  - 2004: Revised Guidelines
Clinical criteria to identify HNPCC/LS families
- Developed in 1991
- Modified in 1999 to include extra-colonic cancers

3-2-1 rule
- 3 first-degree relatives
- 2 successive generations
- 1 under the age of 50

AC II still do not detect 1/3 of HNPCC/LS families
Revised Bethesda Guidelines

- Genetic screening for individuals with:
  1. Families that meet AC II
  2. Two HNPCC related cancers
  3. Colon CA and 1st degree relative with colon or extracolonic cancer <45, adenoma <40
  4. Colon or endometrial CA <45
  5. Right sided colon CA <45
  6. Signet ring colon CA <45
  7. Adenomas <40
Cancer Risks
Cancer Risks

- Colorectal Cancer
- Endometrial Cancer
- Ovarian
- Stomach
- Urinary
- Hepato-biliary
- Small intestine
- Skin (sebaceous tumors)
- Brain

Lynch Syndrome accounts for:

- 3% of colorectal cancer cases
- 3% of endometrial cancer cases

### Lynch Syndrome

#### Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>Lynch Syndrome MLH1 and MSH2 heterozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risks</td>
</tr>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>52%-82%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%-13%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%-12%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
</tr>
<tr>
<td>Pancreas&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;1%</td>
<td>1%-6%</td>
</tr>
</tbody>
</table>


### Table 2. Age-, Sex-, and Country-Specific SIRs and Corresponding 95% CIs by Cancer Site for Carriers and Noncarriers of a Mismatch Repair Gene Mutation Compared With the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>Median (years)</th>
<th>Range (years)</th>
<th>SIR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>16</td>
<td>0.78</td>
<td>49</td>
<td>26-75</td>
<td>20.48</td>
<td>11.71 to 33.27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>6</td>
<td>0.20</td>
<td>53</td>
<td>42-68</td>
<td>30.62</td>
<td>11.24 to 86.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ovary cancer</td>
<td>3</td>
<td>0.16</td>
<td>52</td>
<td>45-56</td>
<td>18.81</td>
<td>3.88 to 54.95</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal cancer*</td>
<td>3</td>
<td>0.27</td>
<td>71</td>
<td>70-77</td>
<td>11.22</td>
<td>2.31 to 32.79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pancreas cancer</td>
<td>2</td>
<td>0.19</td>
<td>64</td>
<td>63-85</td>
<td>10.68</td>
<td>2.68 to 47.70</td>
<td>.001</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2</td>
<td>0.20</td>
<td>59</td>
<td>31-93</td>
<td>9.78</td>
<td>1.18 to 35.30</td>
<td>.009</td>
</tr>
<tr>
<td>Urinary bladder cancer</td>
<td>2</td>
<td>0.21</td>
<td>62</td>
<td>55-68</td>
<td>9.51†</td>
<td>1.15 to 34.37</td>
<td>.009</td>
</tr>
<tr>
<td>Breast cancer‡</td>
<td>7</td>
<td>1.77</td>
<td>56</td>
<td>42-62</td>
<td>3.95</td>
<td>1.69 to 8.13</td>
<td>.001</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>3</td>
<td>1.21</td>
<td>54</td>
<td>50-62</td>
<td>2.49</td>
<td>0.51 to 7.27</td>
<td>.18</td>
</tr>
<tr>
<td><strong>Noncarriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5</td>
<td>4.88</td>
<td>60</td>
<td>55-73</td>
<td>1.02</td>
<td>0.33 to 2.39</td>
<td>.97</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3</td>
<td>4.68</td>
<td>69</td>
<td>46-75</td>
<td>0.64</td>
<td>0.13 to 1.87</td>
<td>.51</td>
</tr>
<tr>
<td>Breast cancer‡</td>
<td>5</td>
<td>6.95</td>
<td>59</td>
<td>52-75</td>
<td>0.72</td>
<td>0.23 to 1.68</td>
<td>.52</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>9</td>
<td>5.53</td>
<td>67</td>
<td>57-92</td>
<td>1.63</td>
<td>0.74 to 3.09</td>
<td>.18</td>
</tr>
</tbody>
</table>

Abbreviation: SIR, standardized incidence ratio.
*Kidney and renal pelvis.
†Adjusted for family using Jackknife method.
‡For females only.
Etiology
Inherited mutations in Lynch Syndrome

• Mismatch Repair Genes

  – *MLH1*
  – *MSH2*
  – *MSH6*
  – *PMS2*
Mismatch Repair Genes

• Microsatellites
  – Short-tandem repeats of repetitive DNA
  – Error-prone
  – Slippage of DNA polymerase

• Mismatch Repair (MMR)
  – MLH1/PMS2
  – MSH2/MSH6
Microsatellite Instability (MSI)
Mismatch Repair genes are Tumor Suppressor Genes (TSGs)

- Recessive loss of function
- Mutation in both copies required to have deleterious effect
- Mutation in one allele can be inherited in germline, causing inherited predisposition towards developing cancer
Mechanism of TSG Losses (2 hits)

- Mutation (genetic)
- Methylation (epigenetic)
- Deletion (loss of heterozygosity)
Mutations in TSGs

• Point Mutations
  – Missense
  – Nonsense

• Insertions
  – Frameshifts

• Microdeletions
  – Frameshifts
Gene Silencing by Hypermethylation

- DNA methylation - addition of methyl group, no change in DNA sequence (Epigenetic)
- Hypermethylation of CpG islands in gene promoters can lead to inactivation of the gene
- Occurs in nearly every type of neoplasm
Chromosomal Deletions

- Most common mechanism to lose second TSG allele

- Leads to loss of heterozygosity (LOH)

![Diagram showing chromosomal deletions](image)
Germline vs. Somatic

• **Germline**
  - Gametes (sperm, ova)
  - Mutations transmitted to every cell in the organism

• **Somatic**
  - Cells forming the body of an organism (internal organs, skin, bones, blood, connective tissue)
  - Mutations transmitted to clonal descendants only
Two-hit hypothesis
Gene Mutations In Lynch Syndrome Families

- MSH2
- MLH1
- MSH6
- PMS2
Lifetime Cumulative Risk of Cancer varies by Gene Mutation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Colorectal (men)</th>
<th>Colorectal (women)</th>
<th>Endometrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>65%</td>
<td>53%</td>
<td>27%</td>
</tr>
<tr>
<td>MSH2</td>
<td>65%</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>MSH6</td>
<td>69%</td>
<td>30%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Hendricks YM, Gastroenterology 2004
**MSH6 Mutation Carriers**

- Atypical family histories
- Incomplete penetrance
- High risk for EMCA
- Lower risk for colorectal cancer in women
- Older age of onset
- MSI-H, MSI-L, or MSS
Diagnosis
Diagnostic Options

• Tumor tissue (Endometrial or Colorectal cancer)
  – Microsatellite Instability
  – Immunohistochemistry for MMR proteins
  – Methylation of MLH1 gene promoter
  – BRAF V600E mutation analysis

• Germline DNA
  – MMR gene sequencing
  – Gene rearrangements and deletions
Microsatellite Instability (MSI)

- NCI Recommended panel of 5 microsatellite markers
  - Mononucleotide: BAT25, BAT26
  - Dinucleotide: D2S123, D5S346, D17S250

- Definitions
  - MSI-H (high): 2 or more abnormal
  - MSI-L (low): 1 abnormal
  - MSS (stable): none abnormal
Immunohistochemistry (IHC)

- MMR mutations interfere with protein production
- Absent IHC staining is abnormal
- May provide information about MMR defects
IHC: Loss of MMR protein staining
## Patterns of IHC Results

<table>
<thead>
<tr>
<th>MSH2</th>
<th>MSH6</th>
<th>MLH1</th>
<th>PMS2</th>
<th>Sporadic</th>
<th>Germline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Sporadic</td>
<td>Test if MSI-H</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td>MSH2, EPCAM, MSH6</td>
</tr>
<tr>
<td>Positive</td>
<td>-</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td>MSH6, MSH2</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
<td>-</td>
<td>BRAF/Methylation</td>
<td>MLH1</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
<td>Positive</td>
<td></td>
<td>MLH1</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
<td></td>
<td>PMS2, MLH1</td>
</tr>
</tbody>
</table>
**EPCAM (TACSTD1)**

- 3’ deletions in *EPCAM* gene → hypermethylation of MSH2 promoter → MSH2 silencing → Lynch Syndrome

- EPCAM deletions account for 20 – 25% of cases with MSH2 negative IHC but no germline *MSH2* mutation found.

Kempers MJ et al., *Lancet Oncol* 2011
Rumilla K et al., *J Mol Diagn* 2011
BRAF/Methylation of $MLH1$

• *BRAF* V600E mutation indicates $MLH1$ downregulation due to promoter methylation
  – Not consistent with Lynch Syndrome

• Only relevant for colorectal carcinomas

Wang L et al., *Cancer Res*, 2003
Germline DNA Mutation Analysis

• Refer patients with abnormal MSI or IHC results to a genetic counselor
  – Not necessarily LS
  – May be due to epigenetic silencing

• Genetic Testing
  – Germline DNA Sequencing
  – Testing for large rearrangements and deletions of MMR genes
Initial Testing Methodologies

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI Testing</td>
<td>77 – 89%</td>
<td>90%</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>83%</td>
<td>89%</td>
</tr>
</tbody>
</table>

- Both MSI testing and IHC are cost-effective
- No data to establish which strategy is optimal
- MSI testing particularly helpful when family history is not strongly suggestive of LS
  - MSS tumor in young patient with negative FH is likely sporadic
  - Patients meeting AC with MSS tumor → 29% have LS
  - Patients meeting AC with MSI-H tumor → 88% have LS
- IHC predicts which gene is mutated and directs sequencing

Palomaki GE et al., *Genet Med* 2009
Langerstedt Robinson K et al., *JNCI* 2007
Who should we test?

• Amsterdam Criteria
  – 50% of families meeting criteria will have LS
  – 68% of patients with LS do not meet AC

• Bethesda Guidelines
  – Broader criteria for testing CRC for MSI
  – MSI detected in 29% meeting criteria. 65% with MSI had *MLH1* or *MSH2* mutation detected

Vasen HF et al., *J Clin Oncol* 2000
Barneston RA et al, *NEJM* 2006
Who should we test?

• Universal or reflex testing of all colorectal and endometrial cancers
  – Found to be cost effective for colorectal cancer
  – Endorsed by EGAPP working group at the CDC

Mvundura M et al., *Genet Med* 2010

• Need to establish institutional infrastructure
Why should we test?

• Enhanced cancer surveillance

• Prophylactic risk-reducing procedures

• Identification of family members with LS
  – Test for known MMR mutation
  – Non-carriers are at average population risk
Screening
Colorectal cancer screening

• Colonoscopy
  – Start age 20 – 25 or 2 – 5 years younger than earliest diagnosis age in family
  – Repeat every 1 – 2 years

• Average age of CRC onset is later for MSH6 and PMS2
  – Can individualize, delay screening until age 30

• Reduces cancer incidence and mortality

Lindor NM et al., JAMA 2006
Gynecologic cancer screening

• Gynecologic cancer risk
  – Risk of endometrial cancer: up to 60%
  – Risk of ovarian cancer: 12%

• No clear evidence to support routine screening
  – May consider annual endometrial biopsy
  – Routine transvaginal ultrasound and CA125 not endorsed: not sufficiently sensitive or specific
Screening for other cancers

- **Gastric cancer**
  - Lifetime risk ranges from 2% - 30%
  - Most cases occur after age 40
  - Stronger predisposition in male patients
  - No clear evidence to support screening
    - May consider EGD extended to distal duodenum or into jejenum every 2 – 3 years starting at age 30 – 35

- **Small bowel cancer**
  - Lifetime risk: 4% - 8%
  - No clear evidence to support screening
    - May consider non-invasive capsule endoscopy
Screening for other cancers

• Urothelial cancers
  – Consider annual urinalysis starting at age 25 – 30

• Pancreatic cancer, brain cancer
  – Lack of data for specific screening
  – Annual history and physical exam at age 25 – 30
Colectomy

• Adenomatous polyps
  – Endoscopic polypectomy with follow-up colonoscopy every 1 – 2 years

• High-grade dysplasia
  – Total abdominal colectomy with ileorectal anastomosis recommended
  – Segmental or extended segmental colectomy may be considered based on individual considerations and discussion of risks

NCCN Guidelines
Hysterectomy/BSO

• Mean age of endometrial cancer diagnosis is 50 years

• Offer after childbearing complete

• Risk of finding occult malignancy
  – Preoperative endometrial biopsy
  – Gynecologic oncology back-up

Schmeler KM et al., NEJM 2006
Prevention
Aspirin reduces incidence of LS-associated cancer

- CAPP2 trial
  - 861 pts with LS
  - Aspirin 600 mg daily vs. Placebo

- Daily ASA > 2 years
  - Decreased CRC
  - Decreased LS-cancer

Burn J et al., Lancet 2011
Conclusions

- Lynch Syndrome (LS) accounts for
  - 3% of colorectal cancers
  - 3% of endometrial cancers

- LS is caused by a mutation in a DNA mismatch repair gene
  - *MSH2* and *MLH1* mutations account for 90% of families
  - *MSH6* mutations cause greater risk for endometrial cancer at a later age of onset

- LS can be diagnosed by
  - Screening tumor with IHC and/or MSI testing
  - Germline DNA testing for DNA MMR gene mutations

- Patients with LS should undergo heightened cancer screening and consider prophylactic surgery

- Daily aspirin may decrease the risk of LS-associated cancer
Thank You!