Gynecologic Cancer in Women with Lynch Syndrome

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Objective

1. To review the life-time risk of gynecologic cancer
2. To review potential symptoms of gynecologic cancer
3. To discuss data and controversies of screening for gynecologic cancer
4. To discuss data on risk-reducing surgery
Lynch Syndrome

- Lynch Syndrome (LS) is an inherited cancer susceptibility syndrome
- Characterized by familial clustering of cancers (e.g. colorectal, endometrial)
- Autosomal dominant genetic defects in mismatch repair genes (MMR)
  - MLH1, MSH2, MSH6, PMS2
- 3-5% of unselected women with EC have LS

# LS–Associated Lifetime Risk of Cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>Lynch Syndrome</th>
<th>MLH1 and MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>6%</td>
<td>40-50%</td>
<td>40-80%</td>
<td>10-22%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>30-60%</td>
<td>25-60%</td>
<td>16-26%</td>
<td>15%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.7%</td>
<td>12%</td>
<td>4-24%</td>
<td>1-11%</td>
<td>-</td>
</tr>
</tbody>
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NCCN Guidelines Version 1.2013
Endometrial Cancer and LS
Endometrial Cancer and LS

- EC is often the first cancer or “sentinel” cancer in LS¹
- Significant lead time before 2nd cancer
- Opportunity to impact patient and family members with CRC screening and risk-reducing surgery²,³
- Difficult to identify women with EC at risk for LS:
  - Criteria for LS colorectal-based
  - Dependence on detailed family history
  - 2/3 with EC would not be identified⁴,⁵

Endometrial Cancer and LS

- Median age of developing EC significantly younger
  - median age late 40’s compared to age 63
- Similar types of endometrial cancer as in sporadic EC
  - 20% high risk type of cancer; may require chemotherapy or radiation
- Similar stage distribution - 80% stage I
- Often associated with symptoms:
  - Postmenopausal bleeding
  - Bleeding between periods
  - Heavy periods
  - Irregular periods
Ovarian Cancer and LS

Stage IIIIC Cancer

- Tumors throughout the pelvis
- Bladder
- Ovary
- Uterus
- Sigmoid colon

Multiple lymph node metastasis

Cancer has spread to the lymph nodes
Ovarian Cancer and LS

- Median age of developing OV is significantly younger than median age early 40’s compared to early 60’s
- Unlike sporadic or other cancer syndromes, different type of ovarian cancer: endometrioid, clear cell type
- Different stage distribution- 80% stage I (70% stage III/IV for sporadic)
- Often picked up incidentally at surgery for EC
- May have better prognosis than sporadic OC likely due to early stage at diagnosis
- May have more predictable progression from early stage to advanced stage compared to sporadic or BRCA OC
Gynecologic Symptoms that Need Investigation

- **Endometrial**
  - Postmenopausal bleeding
  - Bleeding between periods
  - Heavy periods
  - Irregular periods

- **Ovarian** (symptoms almost daily for > 2-3 weeks)
  - Bloating
  - Pelvic or abdominal pain
  - Difficulty eating or feeling full quickly
  - Urinary symptoms (going often or having urgency)

- These symptoms are non-specific and may be due to other non-cancer causes
What Investigations Should be Performed for these Symptoms?

• Abnormal or Postmenopausal Bleeding:
  – **ENDOMETRIAL SAMPLE** (in office biopsy preferred or D&C if no delay)
  – Ultrasound - but should not delay sampling of endometrium
  – Sometimes need to advocate for yourself to get to MD that can do these tests

• Bloating, abdominal/pelvic pain, difficulty eating or urinary symptoms:
  – **ULTRASOUND** - to assess ovaries/pelvis/abdomen
  – +/- CA 125 depending on ultrasound results
In Office Endometrial Biopsy
Transvaginal Ultrasound

Transvaginal Ultrasound

Ultrasound Transducer

Vagina

Sound Waves

Ovary

Uterus

Cervix
Screening for Gynecologic Cancer in Women with Lynch Syndrome

• Ideally want to find precancerous or very early cancerous lesions to minimize morbidity of treatment (requiring less extensive therapy) and decreasing mortality

• We have evidence that CRC screening in the general population and in individuals with LS decreases CRC-related deaths and morbidity (finding precancerous lesions)
Screening for Endometrial Cancer

- There is an early precancerous lesion and a stepwise development from precancer to cancer for most types of endometrial cancer.
- Therefore there is potential that screening could find these early lesions and offer benefit by minimizing treatment and preventing advanced cancer diagnosis.
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Screening for Endometrial Cancer

• No data on EC screening in the general population to guide us:
  • Low prevalence of disease
  • High rate of PMB as an early symptom resulting in early stage of diagnosis with excellent prognosis

• Minimal data in women with LS:
  • Average age of women with EC are premenopausal so abnormal bleeding symptoms not as reliable
  • Higher prevalence of disease
  • May have benefit in this population but very few studies
Screening for Endometrial Cancer

- Only 2 prospective studies which looked at ultrasound with endometrial sampling:
  - Increased rate of precancer and cancer when endometrial sampling is added yearly
  - 66-100% of these lesions would be missed if ultrasound used alone
  - No data on whether lives will be saved or if women will undergo less treatment by participating in EC screening
Screening for Ovarian Cancer

- Excellent evidence in the general population and in other high risk populations (BRCA1/2 mutation carriers) that there is No Benefit of screening for OC with ultrasound and CA125

- Actual increase rate of complications secondary to investigating false positive test results

- These results likely due to the fact that:
  - Most present with advanced stage disease
  - No preclinical lesion identifiable with current screening methods
Screening for Ovarian Cancer in Lynch Syndrome

- **Is OC a different disease in LS?**
  - Different histology
  - More present with early stage is there a longer preclinical stage
- **Could there be a benefit in this population?**
  - Lower prevalence of disease compared to BRCA1/2
  - Small # of women with LS
- **Significant rate of interval cancers which may give false sense of security**
Consensus Guidelines For Gynecologic Cancer Screening

• No evidence to support screening for EC however annual endometrial sampling is an option and often recommended

• May be circumstances where OC may be helpful but no evidence to support its benefit. Possible screening with transvaginal ultrasound and CA125
What Can Be Done to Prevent Gynecologic Cancer?

• Study that compared women who had risk-reducing surgery (removal of ovaries and uterus) to those women who had not had surgery

• No cases of gynecologic cancer in those that had surgery

• 33% developed EC and 5% developed OC in the non-surgery group

• EC median age 46 years and OC median age 42 years
Risk-Reducing Surgery

- **Strong recommendation that women undergo risk-reducing surgery when completed child-bearing**
- Removal of uterus and ovaries by age 40 b/c cancer risk significantly increases after age 40
- Difficult to give recommendations based on specific mutation
- If no cancer history can replace hormones with estrogen until approximate age of natural menopause
Risk Reduction for Gynecologic Cancer

Lynch Syndrome

Surveillance - Followed by Expert in LS

- Investigate Symptoms to rule out cancer
- Age 30 to 40 and wants fertility preservation
- < 30 years old depending on age of family member with GC

Risk-Reducing Surgery

- Completed Having Children
- > 40 years of age
Conclusion

- All abnormal symptoms need to be investigated b/c of increased risk of EC/OC
- No documented benefit of routine surveillance for women with LS
- Good evidence that risk-reducing surgery (removal of ovaries and uterus) will prevent cancer
- Surveillance only as a temporary measure for those who have not completed child-bearing
- Hormone replacement can be given after risk-reducing surgery