Hereditary Breast and Colon Cancer

Presented by Ann Stapleton, RN
Nurse Practitioner

- 23 pairs of chromosomes
- Chromosome is a strand of DNA
- Genes are segments on the DNA
- 30-40,000 genes
Genes are the Units of Inheritance

Adapted from Understanding Gene Testing, National Institutes of Health, 1996.
All Cancer has a Genetic Component
Cancer Mutations

Sporadic

or

Hereditary

Sporadic Cancer

- Acquired during a lifetime
- Age
- Environmental
- Not passed to offspring
Hereditary Cancer

- Less than 10% of cancers
- Germline mutation (present in the reproductive cells) can be passed on to next generation
- Cancers usually occur at younger ages

Family History of Hereditary Breast and Ovarian Cancer

- Hereditary
  - Two or more family members with breast cancer before age 50 or ovarian cancer at any age
  - One family member with breast cancer before age 50 or ovarian cancer at any age, plus Ashkenazi ancestry

- Sporadic
  - None of the breast cancer is diagnosed before age 60
  - No ovarian cancer
  - No clear pattern on one side of family or other

*New Engl J Med 2000;342:564-571*
The Development of Hereditary Cancer

In hereditary cancer, one damaged gene is inherited.

Cancer Genes

- Oncogenes
- Tumor Suppressor Genes
- Mismatch Repair Genes
Oncogenes

- Promotes inappropriate cell proliferation
- "Gas Pedal" is stuck in motion
- Usually not a germline mutation since it is not compatible with life and lethal to embryo
- Exception is a mutation on the RET gene, associated with multiple endocrine cancers.

Tumor Suppressor Gene

- Suppresses inappropriate cell proliferation
- "Brakes" on car
- Requires damage to both copies of the gene to result in a tumor growth
Tumor Suppressor Genes: two hits required

Normal suppressor gene alleles, brakes function fine

One suppressor gene allele mutated, accident waiting to happen

Two suppressor gene alleles mutated, disaster

Mismatch Repair Gene

- Mutations in these genes lead to inefficient repair of DNA
- The “mechanic” is incompetent.
Hereditary Breast Cancer

Hereditary Breast and Ovarian Cancer

Most cases caused by a *BRCA1* or *BRCA2* mutation
Autosomal Dominant Inheritance

Father with mutation on one chromosome

Each child has a 50% chance of inheriting an autosomal dominant disorder

BRCA1 and BRCA2 are Tumor Suppressor Genes

- Protein products of these genes interact with each other in a pathway that repairs damaged DNA
  - Repair of DNA damage prior to cell division is an important way of suppressing tumor development

- BRCA1 and BRCA2 mutations are usually present only in hereditary cancers
“Red Flags” for Hereditary Breast and Ovarian Cancer

- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Multiple primary cancers
- Ashkenazi Jewish ancestry
- Relatives of a BRCA mutation carrier

Family History Considerations

- One-half of BRCA carriers inherit the mutation from their father
- Ovarian cancer is a very important indicator
- Early onset breast cancer is more important than the number of affected family members
A BRCA Mutation Increases Breast and Ovarian Cancer Risks

- Breast cancer by age 50: 2%
- Breast cancer by age 70: 8%
- Ovarian cancer by age 70: <1%

General Population vs BRCA Mutation

A BRCA Mutation Increases Risk of Second Breast Cancer

- Breast Cancer after 5 years: Up to 11%
- Breast Cancer by age 70: Up to 11%

General Population vs BRCA Mutation
Risks in Men With a BRCA Mutation

- Breast Cancer by age 80: <1% in General Population, 7% in BRCA Mutation
- Prostate Cancer by age 80: <1% in General Population, 15% in BRCA Mutation

*Risks refer to BRCA2 mutation carriers. Risks for male BRCA1 mutation carriers are less characterized.

Risks of Other Cancers

- Pancreatic
- Colon
- Melanoma

*Risks are not as high as they are for breast and ovarian cancer.

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Managing Hereditary Cancer Risk

Improved outcomes with proven medical interventions*

- Surveillance
- Chemoprevention
- Prophylactic surgery

*Individual risk reduction may vary based on personal health history

Surveillance for Breast Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 yrs</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 yrs</td>
<td>6 months to a year</td>
</tr>
<tr>
<td>Mammography</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
<tr>
<td>MRI</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Chemoprevention of Breast Cancer

Tamoxifen

- Affected BRCA carriers: 75% decrease for contralateral breast cancer
- Unaffected BRCA2 carriers: 62% decrease
- Unaffected high-risk: 45% decrease
- Aromatase inhibitors are currently under investigation

Prophylactic Mastectomy

Greater than 90% breast cancer risk reduction in BRCA carriers

- Total (simple) mastectomy more effective than subcutaneous mastectomy

References:
Lancet 2000;356:1876-81
JAMA 2001;286:2251-6
JNCI 1998; 90:1371-88
NEJM 2001;345:159-64
JCO 2001;19:1633-7
BJC 93(3):287-92
Surveillance for Ovarian Cancer

- CA-125
- Pelvic exams
- Transvaginal ultrasound

Additional screening techniques under investigation due to limited efficacy of current options

Chemoprevention of Ovarian Cancer

Oral Contraceptives

- Up to 60% risk reduction for ovarian cancer
- Current literature supports there is no evidence that current low-dose oral contraceptive formulations increase the risk of early onset breast cancer for mutation positive individuals
Prophylactic Oophorectomy

Recommend bilateral salpingo-oophorectomy (BSO) at age 35 or after childbearing is complete

- ~96% ovarian cancer risk reduction in BRCA carriers
- Can reduce breast cancer risk by up to 68%

Medical Management in Male BRCA Carriers

<table>
<thead>
<tr>
<th>Site</th>
<th>Procedure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Clinical breast exam</td>
<td>Yearly</td>
</tr>
<tr>
<td></td>
<td>Breast self-exam</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>Mammography</td>
<td>Based on Clinical Findings</td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostate-specific antigen testing</td>
<td>Yearly</td>
</tr>
<tr>
<td></td>
<td>Digital rectal exam</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

NEJM 2002;346:1609-15

JCO 2004;22:735-42
www.nccn.org
## Prevalence of BRCA Mutations

<table>
<thead>
<tr>
<th>Patient's History</th>
<th>Family History</th>
<th>Ovarian cancer in one relative, no breast cancer &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast or ovarian cancer</td>
<td>No breast cancer &lt;50 or ovarian cancer</td>
<td>3.1%</td>
</tr>
<tr>
<td>Breast cancer &lt;50</td>
<td>Breast cancer &lt;50, no ovarian cancer</td>
<td>6.9%</td>
</tr>
<tr>
<td>Ovarian cancer, no breast cancer</td>
<td>Ovarian cancer, no breast cancer</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

[www.myriadtests.com/brcacalculator](http://www.myriadtests.com/brcacalculator)

## Prevalence of Mutations in Ashkenazi Jewish Individuals

<table>
<thead>
<tr>
<th>Patient's History</th>
<th>Family History</th>
<th>Ovarian cancer in one relative, no breast cancer &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast or ovarian cancer</td>
<td>No breast cancer &lt;50 or ovarian cancer</td>
<td>6.6%</td>
</tr>
<tr>
<td>Breast cancer &lt;50</td>
<td>Breast cancer &lt;50, no ovarian cancer</td>
<td>12.2%</td>
</tr>
<tr>
<td>Ovarian cancer, no breast cancer</td>
<td>Ovarian cancer, no breast cancer</td>
<td>23.1%</td>
</tr>
</tbody>
</table>

[www.myriadtests.com/brcacalculator](http://www.myriadtests.com/brcacalculator)
Identifying and Managing Hereditary Colorectal Cancer

Epidemiology of Colorectal Cancer

- Sporadic (~60%)
- Familial (~30%)
- Rare Syndromes (~4%)
- FAP (~1%)
- MAP (~1%)
- HNPCC (3-5%)
Hereditary Colorectal Cancer (CRC) Syndromes

Nonpolyposis (few to no adenomas)
HNPCC – CRC and/or endometrial cancer (EC)

Polyposis (multiple adenomas)
FAP – Severe colonic polyposis +/- CRC
AFAP – Less severe colonic polyposis +/- CRC
MAP – Varying degrees of colonic polyposis +/- CRC

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

MLH1
MSH2
MSH6

HNPCC (3-5%)
Other

Cancer 1996;78:1149-67
“Red Flags” for HNPCC

- Early onset colorectal cancer (<50y)
- Early onset endometrial cancer (<50y)
- Two or more HNPCC cancers in an individual or family*

*HNPCC cancers: colorectal, endometrial, gastric, ovarian, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, sebaceous adenoma

HNPCC Increases Colorectal and Endometrial Cancer Risks

- General Population
- HNPCC

CRC by age 50: 0.2%, Up to 25%
CRC by age 70: 2%, Up to 80%
EC by age 50: 0.2%, Up to 71%
EC by age 70: 1.5%, Up to 71%

Gastroenterology 1996;110:1020-7
Int J Cancer 1999;81:214-8
Gastroenterology 2004;127:17-25
HNPCC Increases Ovarian and Gastric Cancer Risks

- Additional cancers that have a lifetime risk of <5%
  - Ureter/renal pelvis
  - Biliary tract
  - Small bowel
  - Pancreas
  - Brain
  - Sebaceous adenoma

*Int J Cancer* 1999;81:214-8

Gastroenterology 1996;110:1020-7
*Int J Cancer* 1999;81:214-8
HNPCC Increases Risk of Second Cancer

![Bar chart showing risk of cancer within 10 years and within 15 years for General Population and HNPCC.]

Managing Cancer Risk in HNPCC

*Improved outcomes with proven medical interventions*

- Surveillance
- Surgery

References:
- Cancer 1977;40:1849
- Dis Colon Rectum 1986;29:160
- Cancer 1993;36:389-93
- Gastroenterology 2000;118:829-34
- Gastroenterology 2001;121:195-7
- Dis Colon Rectum 2002;45:1588-94
HNPCC Surveillance Guidelines

<table>
<thead>
<tr>
<th>Site</th>
<th>Procedure</th>
<th>Age to Begin</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colonoscopy</td>
<td>20-25</td>
<td>1-2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>Annually</td>
</tr>
<tr>
<td>Endometrium &amp; Ovaries</td>
<td>Endometrial aspiration</td>
<td>25-35</td>
<td>1-2 years</td>
</tr>
<tr>
<td></td>
<td>Transvaginal ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CA-125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HNPCC Surgical Guidelines

- Colorectal cancer or more than one advanced adenoma
  - Colectomy
    - With ileorectal anastomosis (IRA)
    - May be considered for patients unable/unwilling to undergo frequent colonoscopies
  - Hemicolectomy
    - With yearly colonoscopy
- Endometrial/Ovarian cancer
  - Hysterectomy/salpingo-oophorectomy
  - Option for HNPCC patients at time of any intra-abdominal surgery
  - Option after childbearing is complete

JAMA 1997;277:915-19
Gastroenterology 2000;119:837-63
Gastroenterology 2001;121:198-213
Gastroenterology 2003;124:544-60
Dis Colon Rectum 2003;46:1004-12
Hereditary Colorectal Cancer (CRC) Syndromes

Polyposis (multiple adenomas)
- Familial adenomatous polyposis (FAP)
  - Severe colonic polyposis +/- CRC
- Attenuated FAP (AFAP)
  - Less severe colonic polyposis +/- CRC
- MYH-associated polyposis (MAP)
  - Varying degrees of colonic polyposis +/- CRC

Adenomatous Polyposis Syndromes

The majority of adenomatous colonic polyposis is caused by mutations in either the APC or MYH genes.
“Red Flags” for Adenomatous Polyposis Syndromes

- Multiple colorectal adenomas
- Colorectal cancer associated with multiple adenomas
- Possible extracolonic manifestations
  - Non-colonic polyps and cancers (i.e. duodenal, gastric)
  - Desmoid tumors, osteomas, soft tissue tumors, dental abnormalities, CHRPE

Adenomatous Polyposis Syndromes Increase Colorectal Cancer Risk

Cancer risks for MAP are currently unknown, but thought to be significantly elevated.

Am J Pathol 2003;162:1545-8
Int J Cancer 2004;109:594-8
Adenomatous Polyposis Syndromes Increase Risks of Other Cancers

- Additional cancers that have a lifetime risk of <12%
  - Duodenal and periampullary
  - Thyroid
  - Pancreatic
  - Hepatoblastoma (childhood)
  - CNS (medulloblastoma)
  - Gastric
  - Bile duct
  - Adrenal gland

Adenomatous Polyposis Syndromes Surveillance Guidelines

<table>
<thead>
<tr>
<th>Site</th>
<th>Procedure</th>
<th>Age to Begin</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon and rectum (FAP)</td>
<td>Sigmoidoscopy</td>
<td>10-12</td>
<td>Annually</td>
</tr>
<tr>
<td>Colon and rectum (AFAP)</td>
<td>Colonoscopy</td>
<td>Late teens or early 20s</td>
<td>1-3 years</td>
</tr>
<tr>
<td>Stomach/duodenum</td>
<td>EGD</td>
<td>20-25 or time of diagnosis</td>
<td>1-3 years</td>
</tr>
</tbody>
</table>

Surveillance for those with MAP should be similar to that of FAP/AFAP
Adenomatous Polyposis Syndromes
Surgical Guidelines

- FAP (severe polyposis)
  - Colectomy or proctocolectomy
  - Optional post-surgery chemoprevention
  - Post-surgery surveillance for rectal and extracolonic tumors

- AFAP (less severe polyposis)
  - Colectomy may be necessary depending on polyp burden

- MAP
  - Surgical options should be based upon polyp burden

Genetic Testing
American Society of Clinical Oncology
Guidelines for Genetic Testing

- Personal or family history features suggestive of a genetic cancer susceptibility condition
- Test can be adequately interpreted
- Test results will aid in diagnosis or influence medical management of the patient and/or family

Interpreting Test Results

- Positive for a deleterious mutation
- No mutation detected
  - Mutation previously identified in the family
  - No known mutation in the family
- Genetic Variant of Uncertain Significance
Insurance Coverage of Genetic Testing

- Most insurers provide coverage for genetic testing
- Established guidelines
  - Medicare
  - Most major carriers

Genetic Discrimination
Myth Versus Reality

- Federal and state laws prohibit the use of genetic information as a ‘pre-existing condition’
  - Federal HIPAA legislation
  - Majority of states have additional laws
- Over 100,000 tests for hereditary susceptibility to cancer performed to date
- No well-documented cases of genetic discrimination

AJHG 2000;66:293-307
Benefits and Limitations of Genetic Testing

- **Benefits**
  - Allows for individualized medical management
  - Accurate risk assessment
  - Alleviates uncertainty and anxiety

- **Limitations**
  - Positives and true negatives are most informative results
  - Genetic testing does not identify all causes of hereditary CRC

Remember.... genetic testing is a “family affair”
In Summary

1. Screen for “Red Flags”
2. Discuss genetic testing options
3. Establish appropriate medical management plan

Knowledge is Power… And Hope.
Case Presentations
Hereditary Colorectal Cancer

HNPCC Family History
without genetic testing

○ = Cancer
○ = At risk?

EC, dx 35
CRC, dx 59
CRC, dx 28
3 mos
3

28
CRC, dx 28

CRC, dx 59

EC, dx 35

33
HNPCC Family History after genetic testing

FAP Family History without genetic testing
FAP Family History
after genetic testing

CRC, d. 36
? polyps

CRC, dx. 32
100s of adenomas

13
11

34

○ = Cancer
○ = At risk?
○ = Population risk
○ = Mutation positive