Does Cancer Run in Your Family?

Nancie Petrucelli, MS, CGC
Clinical Assistant Professor
Certified Genetic Counselor/Coordinator
Cancer Genetic Counseling Service
Karmanos Cancer Institute
Wayne State University School of Medicine
Objectives

- Review Hereditary Cancer
  - Red Flags
- Discuss A Common Hereditary Cancer Syndrome
  - Clinical Features
  - Medical Management
- Genetic Testing for Hereditary Cancer
  - Caveats and Misconceptions
Cancer is a common disease.

1 of 3 North Americans will develop some type of cancer in their lifetime.
Chromosomes Are Found in Each Cell
Genes (DNA) Comprise Each Chromosome
CHROMOSOME SPREAD
NORMAL FEMALE
46,XX
NORMAL MALE
46,XY
Changes in the DNA message are called mutations

AGCC T AGCA
TCGGG TCGT

Some mutations are "silent"
Some mutations cause disease
• All Cancers are **GENETIC**

**BUT**

• Not All Cancers are **INHERITED**
Sporadic vs. Hereditary Cancer

**Acquired**
- Somatic mutation
  - Carcinogens
  - Aging Process
  - Chance mistake during cell division

**Inherited**
- Germ line mutation
- Runs in the family
Sporadic Cancers

AA → AA

1 “hit” due to chance mistake, carcinogen, etc.

No cancer
Sporadic Cancers

$AA \rightarrow AA$

2nd "hit" in **same cell** due to chance mistake, carcinogen, etc. ......... may become cancer

Genetic, not inherited

not in the gametes
Inherited Cancer Susceptibility

A

One “hit in every cell"
Inherited Cancer Susceptibility

Only one hit needed to possibly cause cancer

Genetic and inherited
Sporadic vs. Hereditary Cancer

Cancer Patients

- Sporadic 85%
- Familial 5-10%
- Hereditary 5-10%
Who Is at High Risk of Hereditary Cancer?

Hereditary cancer accounts for only a small proportion of all cancer.


Cancer Family History

Provides the key to
- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
Three-Generation Pedigree

German/Polish

- d. 70
- Breast Ca, dx 49, d. 52

- Breast Ca, dx 41, 62

English/Irish

- d. 80
- d. 85

- 55, Diabetes, dx 45, 59

- 52

- 35, 30

Features of Hereditary Cancer

- 2 close relatives with the same cancer
- 2 relatives with related cancers (breast and ovarian, colon and uterine)
- Early age of onset (< age 50)
- Bilateral disease

Features of a SPORADIC cancer
- One or only a few affected relatives
- Caused by somatic, not inherited mutations
- Onset usually later in life

Features of a FAMILIAL cancer
- Clusters of cancer in a family
- Genetic predisposition is not clearly evident from family history but needs in-depth evaluation

Features of a HEREDITARY or inherited cancer
- Many affected relatives in several generations
- Caused by germline (inherited) mutations
- Onset of cancer may be early in life
- Bilateral (both sides) cancer of paired organs (kidneys, breasts, adrenal glands, etc.)
- Many different organs may be affected with cancers
Features of Inherited Cancers

- Several relatives with the same or related cancers (breast and ovarian, colon and endometrial)
- Younger age of onset than is typical (< 50 years of age)
- Autosomal dominant pattern of cancer
  - Incomplete penetrance, small family size, young ages of the majority of family members, few at-risk women
- Presence of rare cancers (male breast cancer)
- Excess of multifocal or bilateral cancers
- Excess of multiple primary cancers
- Presence of other nonmalignant features
  - Colon polyps
- Certain Ethnicities (Ashkenazi Jewish)
Family History is Always Changing

Initial History

- Ovarian, 54

2 years later

- Breast Ca, 44
- Melanoma, 48

Adapted from ASCO
Key Points

- Only 5-10 percent of cancer is hereditary (due to a single germline mutation)
  - Genetic testing is not a screening test for the general population
- Family history is the most important tool in assessing one’s risk for hereditary cancer
- Being aware of the following information in your family will allow you to determine if you may be at-risk for hereditary cancer
  - *Who in the family has had cancer?*
  - *What types of cancer?*
  - *Around what age were relatives diagnosed (> or < age 50)*
Hereditary Breast and Ovarian Cancer Syndrome
How Much Breast and Ovarian Cancer Is Hereditary?

Breast cancer:
- Sporadic: 85%–90%
- Family clusters: 5%–10%
- Hereditary: 15%–20%

Ovarian cancer:
- Sporadic: 90%–95%
- Family clusters: 5%–10%
- Hereditary: ~10%
Cells have Two Copies of BRCA1 and BRCA2

Adapted from *Tools for Understanding Genetics*
National Human Genome Research Institute
Office of Science Education and Outreach
www.nhgri.nih.gov/DIR/VIP
Clinical Features of Hereditary Breast and Ovarian Cancer Syndrome
A BRCA Mutation Increases Breast and Ovarian Cancer Risks

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>BRCA Mutation</th>
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<tbody>
<tr>
<td>Breast cancer by age 50</td>
<td>2%</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>Breast cancer by age 70</td>
<td>&lt;1%</td>
<td>Up to 87%</td>
</tr>
<tr>
<td>Ovarian cancer by age 70</td>
<td>&lt;1%</td>
<td>Up to 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 27%</td>
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Lancet 1994;343:692-695
NEJM 1997;336:1401-1408
AJHG 2003;72:1117-1130
AJHG 1995;56:265-271
Science 2003: 643-646
JCO 2005 23 (8): 1656-63
NCI 2005
I already know I have breast cancer

Why should I care about her BRCA1/2 status?
Mutations in *BRCA1* and *BRCA2* increase the risk of second cancers, as well as other cancers.
A *BRCA* Mutation Increases Risk of Second Breast Cancer

**Graph:**

- **BRCA1:**
  - Up to 64%
  - Up to 3.5%
- **BRCA2:**
  - Up to 50%
  - Up to 27%
  - Up to 24%
  - Up to 11%
  - Up to 13%
- **General Population:**
  - Up to 1%

**Legend:**

- General Population
- *BRCA* Mutation

**Data Sources:**

- Lancet 1998;351:316-21
- Gynecol Oncol. 2005 Jan;96(1):222-6

**Risk of Cancer (%)**

- Breast Cancer after 5 years
- Breast Cancer by age 70
- Ovarian Cancer within 10 years after breast cancer
Risks in Men With a BRCA Mutation

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

- **Pancreatic cancer by age 80**
  - General Population: <1%
  - BRCA Mutation: Up to 7%

- **Melanoma by age 80**
  - General Population: 2%
  - BRCA Mutation: Up to 4%
Clinical Management of *BRCA1* and *BRCA2* Mutation-Positive Patients

Positive *BRCA1* or *BRCA2* test result

- Identify at-risk adult relatives; offer genetic counseling/testing
- Increased surveillance
- Chemoprevention
- Prophylactic surgery

Modified and used with permission from Myriad Genetic Laboratories Speakers Program.
“Red Flags” for Hereditary Breast and Ovarian Cancer Syndrome

- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Two primary breast cancers in an individual at any age
- Both breast and ovarian cancer in an individual at any age
- Two or more breast cancers in a family, one under age 50
- Ashkenazi Jewish ancestry
- Relatives of a \textit{BRCA} mutation carrier
9/18/2009

cancer? = yes

Finland

73
Prostate 70

81
42
Breast 40

Poland

73
Prostate 74

75
Stomach 71

92
Prostate 88

64
Multiple myeloma 63

68
Colon 64

90

60
Breast 40

Breast 49

BRCA1+

59
Breast 42

57
Dvay 54

36
32
27
Breast 21

25
23

BRCA1-

3
1
2
cancer? = yes

Polish - Ashkenazi Jewish

Russian - Ashkenazi Jewish

Accident

Holocaust

Holocaust

Pancreas 90s

Leukemia

Breast 76

BBCA1/2-

Lung 54

Ovary 56

BBCA2+

BBCA1/2-

Ovary 51

Thyroid 31

Breast 53

Ovary 54

BRCA1/2-
BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

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

185delAG
Prevalence = ~1%

5382insC
Prevalence = ~0.15%

6174delT
Prevalence = ~1.5%

Misconceptions About Family History

- "Cancer on the father’s side of the family doesn’t count."
- "Ovarian cancer in the family history is not a factor in breast cancer risk."
- "The most important thing in the family history is the number of women with breast cancer."

- Half of all women with hereditary risk inherited it from their father.
- Ovarian cancer is an important indicator of hereditary risk, although it is not always present.
- Age of onset of breast cancer is more important than the number of women with the disease.
cancer? = yes

Welsh/Irish/German

French/Canadian/German

81
78
47
Breast 39
Breast 45
BRCA1+

23
20
25
31
27

49
57

47
40
3

76
74

88
Breast 55

9/18/2009

BRCA1+  BRCA1.
Key Points

- Hereditary Breast and Ovarian Cancer (HBOC) accounts for 5-10% of all breast and ovarian cancer cases
- Due to mutations in *BRCA1* and *BRCA2*
- The appropriateness of genetic testing is based on careful assessment of the personal and family history (‘red flags’)
- Some families do not present with classic HBOC ‘red flags’
- Threshold of suspicion is lowered in:
  - Populations at risk (Ashkenazi Jews)
  - Families with a limited family structure (few females)
  - ‘Young’ families
  - Triple negative breast cancers
- HBOC can be inherited from the father (studies suggest HCPs are less likely to refer those with a paternal family history)
When Should Genetic Testing Be Considered?

- Patient has a reasonable likelihood of carrying an altered cancer susceptibility gene
- Genetic test is available that can be adequately interpreted
- Results will influence medical management or aid in the diagnosis of a hereditary cancer syndrome

Genetic Counseling Is Integral to the Testing Process


McKinnon WC et al. JAMA. 1997;278:1217-1220.

If a mutation is found in an affected person, testing will be more informative for other family members.
Genetic Testing Has Implications for the Entire Family

- Consider the impact of testing on all family members
- Ultimately, testing is the individual’s choice

Autosomal Dominant Inheritance

Legend

B: BRCA gene with mutation
b: normal BRCA gene
A Negative Result Is Not Always Easy to Accept

Condition: Li-Fraumeni
Gene: TP53

“I feel so guilty that I was spared”


A “Positive” Result May Relieve Uncertainty

Condition: Li-Fraumeni
Gene: TP53

<table>
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<tr>
<th>Genetic Susceptibility Testing</th>
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<td>Is <em>not</em> a screening test for the general population</td>
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Flunk the Gene Test and Lose Your Insurance
“Genetic Discrimination”

“Discrimination directed against an individual or family based solely on an apparent or perceived genetic variation from the ‘normal’ human genotype.”

This term applies to asymptomatic individuals.

"The perceptions of discrimination far exceed the reality."

*Genetic Testing* 1:91-98, 1997

- Follow-up study of women tested for hereditary breast and ovarian cancer risk found that "none has had medical insurance cancelled or insurance rates raised."

- "Like so-called urban legends that are built on rumor rather than fact, the perception of insurance company bias against patients who undergo predictive genetic testing seems to be largely unsubstantiated."
  - *JAMA* December 15 1999;282:2197-2198

- "We find that there are almost no well-documented cases of health insurers either asking for or using presymptomatic genetic test results in their underwriting decisions."
Health Insurance Portability and Accountability Act (HIPAA) 1997

- Genetic information shall not be considered a preexisting condition
- Prevents insurers from refusing to renew/continue coverage because of genetic information
- Prevents group plans from charging different premiums
- Prohibits plans from using genetic information in determining eligibility for coverage or setting premiums
Genetic Information Non-Discrimination Act (GINA) 2008

- Prevents employers from using genetic information in employment decisions (took effect November 2009)
- Prohibits insurers in both group and individual policies from using genetic information to deny coverage or to set or adjust premiums (took effect May 2009)
- Does not cover life insurance, disability insurance, or long term care insurance policies
Do you really want to know?
Appropriate Candidates for Cancer Genetic Counseling

- Relatives with the same or related cancers
- Relatives who developed cancer at an early age
- Relatives with more than one type of cancer
- Family history of bilateral disease
- Family history of rare or unusual cancers

Anxiety and/or concern about cancer risk
Components of Cancer Genetic Counseling

- Compilation of detailed 3 or more generation pedigree
- Pedigree-based and empiric risk assessment
- Discussion of options for genetic testing, if indicated
- Review of management options for high-risk individuals
- Explanation of testing outcomes and interpretation
- Provision of appropriate referrals
Cancer Genetic Counseling Service
Karmanos Cancer Institute

- Staff
  - Michael Simon, MD, MPH – Director
  - Nancie Petrucelli, MS, CGC – Coordinator
  - Tessa Paling, MS
  - Wanda Sheard – Administrative Assistant

- Clinics
  - Downtown-Main Campus
  - Farmington Hills – Weisberg Cancer Treatment Center

Appointments can be made by calling (313) 576-8748
Summary

- Only 5-10 percent of cancer cases are hereditary.
- Genetic testing is not a screening test for the general population.
- Genetic testing should be considered when a patient has a reasonable likelihood of carrying an inherited cancer susceptibility gene (after careful pedigree analysis and risk assessment).
- Not all inherited cancer families are ‘classic’.
- Caveats to genetic testing exist.
- You have an important role in identifying at-risk patients.
Top Ten Reasons to Know Your Family History

10. It’s a FREE medical screening that you can do in the privacy of your own home.
9. It’s a great way to get to know relatives in older and younger generations.
8. It’s a good way to know your risk for conditions seen in relatives.
7. Because when you need to know, they may not be there to ask.
6. Because with a little help from the past, you can change the future.
5. Because it’s not just recipes that get passed down in families.
4. It’s a priceless gift to leave to your children.
3. It doesn’t cost a thing and it could save your life!
2. Because what you don’t know CAN hurt you.
1. Because every family has a story, but not every family has YOUR story.