Assessing Your Cancer Genetic Risk

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Outline

• Introduction
• Family history
• Ovarian cancer genetic syndromes
  – BRCA1 and BRCA2
  – HNPCC
• Issues in genetic testing
Patient Concerns

- What is the chance I will develop cancer?
- How can I reduce my risk of cancer?
- Am I at risk for another cancer?
- When and what type of screening should I have?
- What is the risk of cancer to relatives?
- How do I talk to my children about their risk of cancer?
Cancer Genetic Counseling

- Pedigree interpretation and cancer risk assessment
- In-depth counseling and education
- Ordering and interpreting genetic test
- Facilitating entry into clinical studies
Genetic Counseling Appointment

- Family history
- Risk assessment
- Counseling-experience with cancer in family
- Education
- Genetic testing?/Decision making
Who Is at High Risk for Hereditary Cancer?

Hereditary cancers account for only a small proportion of all cancer
How Much Cancer is Hereditary?

- Sporadic: 15%-20%
- Family clusters: 5%-10%
- Hereditary
Causes of Hereditary Susceptibility to Ovarian Cancer

- Sporadic
- Hereditary (5%–10%)
  - BRCA1 (~70%)
  - Other single genes (~8%)
  - HNPCC (~2%)
  - BRCA2 (~20%)
Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No “skipped generations”
- Equally transmitted by men and women
Allele Segregation

Alleles: variant forms of the same gene (A a)
CANCER RISK

**High**
- Multiple generations – dominant
- Early onset
- Multiple primary tumors

**Moderate**
- Several family members affected
- No single gene pattern
- Variable onset

**Low**
- No family history
- Late onset
The Cancer Family History
Is the Key to:

- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
Our Family Tree

Grandma

My Mum

Stacey

My Dad

Grandma

Alien family

My sister

James

My sister

Ben

My brother

My sister

Stephen

My sister

My sister

My sister

My baby nephew

My baby Cousin
Taking a Cancer Family History

• Obtain at least a three-generation pedigree
• Ask about all individuals in the family and record:
  – age at cancer diagnosis, age at and cause of death
  – primary vs. metastatic cancer
  – precursor lesions, bilateral cancer
• Record ethnicity and race
Take a 3 Generation Family History
Verify Family History

Verbally reported pedigree

- Stomach Ca
- Bone Ca d. 59
- Prostate Ca

Revised pedigree based on pathology reports

- Ovarian Ca dx 43, d. 49
- Breast Ca dx 45 d.59
- BPH dx 54

BPH = Benign prostatic hyperplasia
When to Suspect Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Evidence of autosomal dominant transmission
How Much Breast and Ovarian Cancer is Hereditary?

Breast Cancer

- Sporadic: 85%
- Family clusters: 15%
- Hereditary: 5%

Ovarian Cancer

- Sporadic: 95%
- Hereditary: 5%
Approximate Carrier Frequency of BRCA1 mutation in the U.S.

- U.S. Citizens
- Ashkenazi Jews
- Female breast cancer patients
- Ashkenazi Jews with breast cancer
- Female with breast cancer under age 30
- Ashkenazi Jews with breast cancer under age 42

Source: 2000 Meeting of the American Society of Clinical Oncologists
Breast dx 45
Ovary, dx 59
d.62

BRCA1 or BRCA2
Hereditary Breast and Ovarian Cancer

Noncarrier
BRCA mutation carrier
Affected with cancer
Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer
BRCA1 and BRCA2 Mutations Increase the Risk of Breast and Ovarian Cancer

Breast Cancer Risk

Ovarian Cancer Risk

Percent of Women With Breast Cancer by Age 70

Percent of Women With Ovarian Cancer by Age 70
Screening for women + BRCA

**Breast**
- Monthly breast self-exams (begin by age 18) and
- Early clinical surveillance (begin at age 25)
  - annual or semi-annual clinical breast exams
  - annual mammography
  - annual MRI (alternating every 6 mos with mammogram)

Modified from: Cancer Genetics Studies Consortium Consensus Statement

**Ovarian**
- No proven methodology
- Annually or semiannually, starting at 25–35
  - transvaginal ultrasound w/color Doppler imaging
  - CA-125
  - Pelvic exam

“There are no data demonstrating that screening these high-risk women reduces their mortality from ovarian cancer. Nonetheless, [these measures] are recommended.”

*NIH Consensus Conference, *JAMA* 273:491, 1995*
Options for BRCA-Mutation Carriers

- Breast cancer screening
- Ovarian cancer screening
- Prophylactic surgery
  - Mastectomy
  - Oophorectomy
The Family History Is Key to Diagnosing HNPCC
Amsterdam Criteria

- 3 or more relatives with verified CRC in family
- One case a first-degree relative of the other two
- Two or more generations
- One CRC by age 50
- FAP excluded

Failure to meet these criteria does *not* exclude HNPCC

Genetic Features of HNPCC

• Autosomal dominant inheritance
• Penetrance ~80%
• Genes belong to DNA mismatch repair (MMR) family
• Genetic heterogeneity (\textit{MLH1, MSH2, MSH6, PMS1, PMS2})
Lifetime risk of developing cancer

- Ovarian
- Endometrial
- Colon

Legend:
- General Population
- HNPCC
Cancer Risks in HNPCC

- Colorectal: 78%
- Endometrial: 43%
- Stomach: 19%
- Biliary tract: 18%
- Urinary tract: 10%
- Ovarian: 9%


ASCO
Points to Remember

Testing Genetic Susceptibility

is not a screening test for the general population

can be one component of a comprehensive cancer risk-assessment plan
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
Breast Ca, 42
Ovarian Ca, 38
d.45

Pretest Genetic Counseling

Test first, if possible

Person seeking counseling (proband)

If a mutation is found in an affected person, testing will be more informative for other family members.
Interpreting a Negative Result

No identified mutation in family

Family with known mutation

Colon Ca, 52

Colon Ca, 45

Endometrial Ca, 47

Colon Ca, 45

Endometrial Ca, 47

No identified mutation in family

Family with known mutation

Colon Ca, 52

Colon Ca, 45

Endometrial Ca, 47

37 MSH2-
Genetic Predisposition Testing Is a Multi-Step Process
Counseling Issues in Cancer Risk Counseling

- Decisions around testing
- Impact of information/results
  - Health management
- Anxiety issues re cancer risk
- Emotional impact of family history
- Notification of relatives
Genetic Counseling for Cancer Genetic Syndrome

Family History

- Genetic testing-Yes
  - Risks and benefits
  - Test interpretation
  - Consent form
  - Cost and insurance coverage
  - Medical management
  - Impact on relatives

- Genetic Testing-No
  - Medical management
  - Cancer risk to relatives based on family history

- Test results
  - Disclosure in clinic
  - Cancer risk based on results

- Follow-up
  - Referrals to additional health care providers
  - Patient’s discussion with relatives
Psychological Issues in Testing

- Anxiety/fear
- Guilt
- Self-esteem
- Depression
- Stigmatization
- Grief and/or anticipatory loss
- Changes in family dynamics
Potential Risks of Genetic Testing

- Psychological distress
- Loss of privacy
- Discrimination by employers and insurers
- Change in family dynamics
- False sense of security
Potential Benefits of Genetic Testing

- Improved cancer risk management
- Relief from uncertainty and anxiety about cancer risk
- Information for individual and family members
- Lifestyle decision making
Common Ethical Issues for Families

- Right to know/right not to know
- Sharing of information
- Coercion
- Privacy
- Reproductive decision making
- Testing of minors
Cancer Risk Assessment: Key Points

- Assess patient’s perception of cancer risk
- Obtain a careful family history that includes at information about age of diagnosis of cancers and primary diagnosis of cancers
- Be aware of appropriate screening recommendations based on family history
- Confirm verbal reports with pathology records when possible
- Appreciate when a family represents a cancer genetic syndrome
- Refer to a genetic counselor for hereditary cancer family issues including genetic testing
Summary

• Most ovarian cancer is not inherited
• Gene mutations in some families
  – BRCA1/2 & HNPCC
• Genetic testing is available for these genes
  – Importance of genetic counseling and correct test interpretation