What All of Us Should Know About Cancer and Genetics

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Objectives

By the end of this presentation, participants will be able to:

- Describe the difference between hereditary predisposition to cancer and non-hereditary cancer.
- Recognize family history clues that are suggestive of a hereditary form of cancer.
- Outline the reasons to consider genetic testing for a hereditary form of cancer as well as reasons to not pursue genetic testing.
Before We Begin

If you had the chance to have genetic testing right now to see if you carried a genetic change that predisposed you to cancer, would you do it?

Yes, Maybe or No?
Overview

- Chromosomes
- Genes
- Gene Mutations
- Basic Cancer Genetics
- Breast/Ovarian Cancer
- Colon Cancer (HNPCC and FAP)
- Family Cancer Syndromes
- The Whys, When, and Who of Genetic Testing
Chromosomes

- Live in the nucleus in the center of our cells
- They contain our genes like a skyscraper contains thousands of rooms inside
- At conception we receive half of our chromosomes (and genes) from our mother and half from our father
- We each have 23 “pairs” of chromosomes
- #1 through #22 are the non-sex chromosomes (called autosomes)
- The last pair is the sex-chromosome pair – XX for girls and XY for boys
The DNA Sequence
Our Genetic Blueprint

- There are only 4 letters in the genetic alphabet.
- Our entire DNA sequence is made up of combinations of four bases (ATCG) with specific pairing of A with T and C with G.
- There are about 23,000 genes and about 10,000 of these genes code for structural proteins, enzymes, and regulatory proteins.
- These proteins are essential for cellular metabolism, organ structure and development, physical growth, thinking and other body functions.
Mutations (1)

- Are permanent changes in the genetic sequence within the DNA – similar to a typographical error.

- A mutation may be passed down from a parent to a child, can arise during egg or sperm formation, or can happen in a single cell in our body on any given day and at any given age.

- When a mutation is present at birth and in all the cells in our body, this is called a GERMLINE MUTATION.

- When a mutation arises after birth in a cell in our body, this is called a SOMATIC MUTATION.
Mutations (2)

A change in the DNA sequence may:

- Prevent a protein from being made altogether
- Produce a protein that is only partially functional
- Produce a protein that works incorrectly and may disrupt an important pathway or even speed up a cellular pathway
When is Cancer Genetic?

- Mutations and other genetic changes within normal cells can result in the cell transforming from a benign (non-cancerous cell) to a malignant (cancerous cell).

- On a cellular level ALL CANCER IS GENETIC.

- But on an individual level relatively few cancers are “inherited” or due to a predisposing genetic change.
When is Cancer Inherited?

About 5% to 10% of all breast/ovarian and colorectal cancer arises in patients born with a genetic predisposition.

BRCA 1 and BRCA 2 mutations are responsible for many of the familial breast and ovarian cancers.

Mutations in one of five or so mismatch repair genes can predispose to colon cancer not associated with large numbers of colon polyps.

There are also a number of less common familial cancer gene syndromes.

Taking a good medical and family history is the key to discovering whether the cancer is familial or just happened by chance.
Who to Test

Many physicians offer genetic testing to a person who has a strong family history of cancer, but has not had cancer himself or herself.

This is NOT the best way to approach testing.

It is best to test, if possible, a person in the family who has had cancer to give the best answer to other family members.
BRCA 1 and BRCA 2

- Two specific tumor suppressor genes that are associated with breast and/or ovarian cancer
- Are inherited as AD traits
- On a cellular level function as a recessive condition due to loss of heterozygosity
Tumor Suppressor Genes

Typical cell with both sets of brakes – front and back. Able to divide and hold cell division to a regular rate. Needs BOTH sets of brakes out before growing out of control.

Mutated cell with only one set of brakes – the back set. Still able to divide and hold cell division to a regular rate. Needs the back set of brakes out before growing out of control.

Badly mutated cell with NO sets of brakes (both front and back brakes are gone). Unable to hold cell division to a regular rate. This cell is now malignant and growing out of control.
My Family and BRCA 1

Bladder CA

Unilateral Br CA
Prostate CA

Bilateral Br CA
Bilateral Br CA

Bilateral Br CA
DNA+

DNA-

2
BRCA 1 Associated Cancers

- Lifetime breast cancer risk is 50 – 85% compared to the general population risk of 10%
- Breast cancer is often early onset with a 40 – 60% risk for a second primary breast cancer
- Lifetime ovarian cancer risk is 15 – 45%
- Slight increased risk for colon cancer as well as prostate cancer in males who carry the gene mutation
BRCA 2 Associated Cancers

- Lifetime breast cancer risk is 50 – 85%
- Risk for breast cancer in males is 6%!
- Lifetime ovarian cancer risk is 10 – 20%
- There appears to be an increased risk for other cancers such as prostate, pancreatic and laryngeal
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

- Accounts for about 5% of all colorectal cancer
- Variable but often early age of onset (<45 years of age)
- Frequently occurs in the proximal or right side of the colon rather than the left
- Is associated with extra-colonic tumors as well such as: ovarian, gastric, urinary tract, small bowel, bile duct or sebaceous glands
Typical HNPCC Family History

- A number of relatives with CRC including a first degree relative
- Seen in more than one generation
- At least one affected person diagnosed before age 50
- Not associated with multiple colon polyps
- Relatives with one or more of the associated extra-colonic tumors
HNPCC Genetics

- At least five distinct HNPCC genes have been identified.
- All appear to be responsible for DNA mismatch repair.
- These genes are: MLH1, MSH2, MSH6, PMS1 and PMS2.
Familial Adenomatous Polyposis (FAP)

- Accounts for only 1% of colorectal cancer
- Patients develop hundreds if not thousands of colon polyps that each has the potential to undergo malignant transformation
- Lifetime risk of CRC is close to 100%
- Other associated tumors include: tumors of the upper GI tract, thyroid and brain
- In a subset of patients, benign tumors of the bone (osteomas) and skin (desmoids) may also be seen
- Some patients have a milder “attenuated” form of FAP
FAP Family History

- For about 70% of patients with FAP there is a family history of CRC in multiple generations or in a first degree relative.
- For the other 30%, FAP may have resulted from a new (de novo) mutation.
- Some individuals who carry an FAP mutation have an unusual eye finding called CHRPE (congenital hypertrophy of the retinal pigment epithelium).
FAP Genetics

- Caused by mutations in the APC gene which is a tumor suppressor gene like BRCA 1 and 2
- Many different mutations have been identified and molecular testing can sometimes be done by a pretty nifty technique known as protein truncation assay
- For adults at risk for FAP, colonoscopy is often diagnostic
Clues to a Possible Heritable Form of Cancer

- Earlier than usual age of onset
- Multiple tumor foci or multiple primary tumors
- Bilateral cancers
- Unusual tumor types
- Multiple affected family members – may follow an AD pattern or occasionally AR
Li Fraumeni Syndrome

- A rare AD cancer syndrome associated with mutations in the TP53 gene
- The lifetime risk for cancer is 90% for female and 70% for male carriers
- Cancer types include:
  - \( B \) - breast
  - \( B \) - bone
  - \( B \) - brain
  - \( L \) - leukemia
  - \( L \) - lymphoma
  - \( A \) - adrenal
  - \( S \) - soft tissue sarcomas
Typical Li Fraumeni Pedigree

- Bil Breast Cancer 40y
- Breast Cancer 35y
- Breast Cancer 37y
- Lymphoma 40y
- Lymphoma 44y
- Osteosarcoma 16y
- Brain Cancer 4y
- Adrenal carcinoma 3y
- Soft tissue sarcoma 7y
When to Consider Cancer Gene Testing

- If we can identify who and who is not at risk in a family
- If patients can take advantage of increased surveillance (i.e. more frequent mammograms), lifestyle changes, therapeutic trials and/or prophylactic surgery (i.e. mastectomy or oophorectomy)
- If we can obtain informed consent
When Not to Consider Cancer Gene Testing

- When knowledge of the carrier state does not change management or surveillance options.
- When the patient is a child and the cancers would not occur until after 18 years of age when the patient can consent for himself or herself.
- When, after careful consideration, the patient does not wish to have this information.
- It is usually not a good idea to do cancer gene testing while in the early stages of chemo or radiation therapy, but rather to wait until the patient is less overwhelmed and can make a rational decision.
So Now How Do You Feel?

If you had the chance to have genetic testing right now to see if you carried a genetic change that predisposed you to cancer, would you do it?

Yes, It Depends, or No?