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Familial Cancer Syndromes

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Summary and Key Points

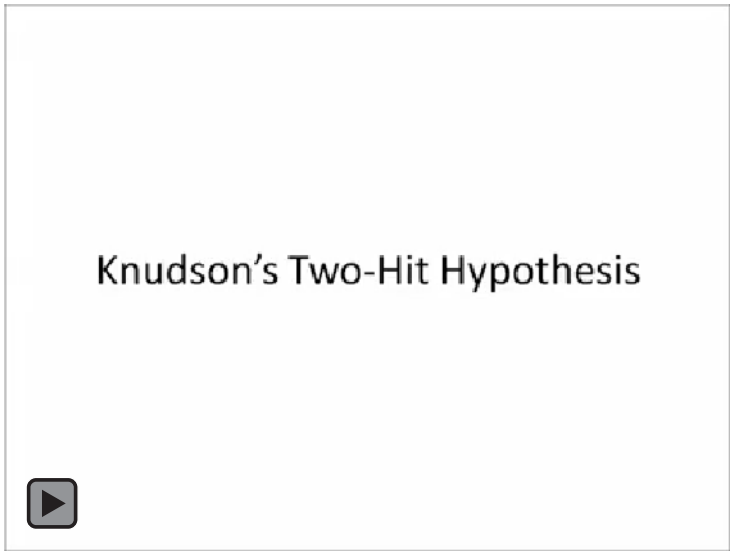
1. Up to 10% of certain cancers are familial.
2. Cancer syndromes are inherited in an autosomal dominant fashion.
3. Inheritance of a familial gene mutation greatly increases the risk of cancer.
4. Identification of cancer syndromes and their genes allows for increased surveillance and/or tailored treatments.

Introduction

While the majority of cancers are not inherited, there are a number of well described collections of cancers that occur within families. These cancer syndromes were initially identified based on observation of family histories and subsequently the molecular mechanisms have been elucidated. This chapter is intended to allow the reader to recognize when a pattern of cancers occurs in an individual or their family, and to generate an investigation into potential cancer syndromes. With the rapidly expanding understanding of the molecular basis of cancers at the cellular and constitutional levels, appropriate preventive care may be offered and tailored treatment holds great promise.

Important Concepts

All cancer is genetic on the cellular level. All tumors, inherited or sporadic, arise from deregulation of genetic instructions intended to keep cells growing and functioning normally. At the cellular level this occurs in a recessive pattern, meaning that somatic damage must occur to both the paternally and maternally inherited copy of the regulatory gene. Cancer predisposition, or the inheritance of a germline mutation increasing likelihood of cancer occurrence, is inherited in a dominant fashion. This is illustrated through Knudson's two-hit hypothesis[1] (Movie 1).



Movie 1. Kudson's Two-Hit Hypothesis. Movie courtesy of University of Massachusetts Medical School, Department of Pediatrics.

Keep in mind that there are genetic tests that look for somatic genetic changes. These somatic changes may inform treatments such as effective chemotherapies. That is why this testing is performed specifically on a tumor. However, genetic testing for cancer predisposition is always performed looking for germline inherited mutations, which is why it is often done on blood samples.

Key features in a family or individual that raise the suspicion for an inherited cancer syndrome include:[4]

- Early onset of cancer
- Multiple primary tumors in the same person (not related to prior treatment)
- Multiple affected family members
- Occurrence of cancer in multiple generations, clustering of related cancers
- Ashkenazi Jewish heritage (specific for BRCA)

Early onset cancer is generally defined as diagnosis at or below the age of 50. The pedigree below (Figure 1) depicts a sample family history that could be applied to any of the following cancer syndromes.

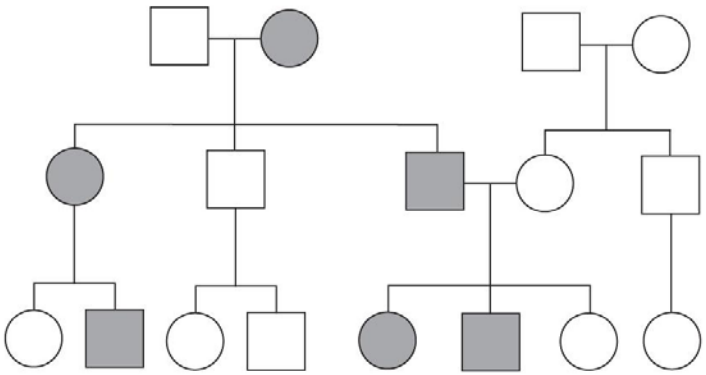


Figure 1. Sample cancer syndrome family history pedigree. University of Massachusetts Medical School, Department of Pediatrics.

The following specific cancer syndromes will be discussed: BRCA, Lynch syndrome, and FAP. Evidence based management guidelines for these conditions are maintained by the National Comprehensive Cancer Network. This group makes up a representative sample of numerous familial cancers, some of which are quite rare.

Hereditary Breast and Ovarian Cancer

BRCA1 & BRCA2

These are tumor suppressor genes which function in the DNA repair pathway.[2] In the general population, the likelihood of a BRCA mutation is 1 in 500. Within the Ashkenazi Jewish population there are 3 founder mutations, which increase the risk to 1 in 40. Inheritance of a mutation in one of these genes increases the risk for the following cancers (in decreasing order): breast (up to 87% by age 70), ovarian (up to 40% by 70), prostate (20%), pancreatic (7%) and melanoma (specific to *BRCA2* mutations). The risk of male breast cancer is also increased to approximately 8%. Early and frequent screenings, as well as select preventive treatments, are available to mutation-positive individuals, the details of which are beyond the scope of this chapter.

Colon Cancer

Lynch Syndrome

Also called Hereditary Nonpolyposis Colorectal Cancer (HNPCC), this disorder is caused by mutations in one of several genes involved in DNA mismatch repair. The genes, listed in order of frequency, are *MLH1*, *MSH2*, *MSH6*, *EPCAM* and *PMS2*. Mutations in one of these genes, most often *MLH1* and *MSH2*, account for 1%-3% of all colon cancers and ~1% of all endometrial cancers. Colorectal tumors excised from patients with Lynch syndrome exhibit microsatellite instability (MSI), and immunohistochemistry staining of the tumor can facilitate targeted testing for these genes. Individuals who have inherited one of these gene mutations are at increased risk for cancer of the colon (80% by age 70), endometrium (60%), stomach (13%), ovary (9%-12%), biliary tract (2%-18%), urinary tract (5%-10%) and brain (1%-3%). Screening modalities are available for colon cancer and prophylactic hysterectomy or oophorectomy may be offered.[3]

It should be noted that the moniker “nonpolyposis” is misleading, since affected individuals have polyps prior to colorectal cancer; the term was used to distinguish Lynch syndrome from Familial Adenomatous Polyposis (FAP). Several sets of guidelines have been used to determine the likelihood of Lynch syndrome in a family or individual, but recent studies argue for broader screening by use of MSI/IHC testing in tumor cells.

Familial Adenomatous Polyposis

While rare, accounting for 0.5%-1% of all colon cancers, FAP demonstrates remarkable penetrance within families. Virtually 100% of individuals with FAP will develop colon cancer unless treated, with diagnosis at the mean age of 39 and with onset of polyps in childhood. Polyps are extensive, numbering in the 100s to 1000s. FAP is caused by mutations of the *APC* gene, the normal function of which appears to be a tumor suppressor with an additional role in colonic cell migration. In addition to colon cancer, affected individuals are at an increased lifetime risk for cancer of the small bowel (4-12%), pancreas (2%), thyroid (1%-2%), liver (~1%) and brain (<1%). Attenuated FAP is characterized by fewer colonic polyps and later onset of cancer (still with significant risk) thought to be correlated to specific *APC* mutations. Non-cancer related findings in FAP include congenital hypertrophy of the retinal epithelium (CHRPE), osteomas, dental anomalies, epidermoid cysts, lipomas, and desmoid tumors. Screening for polyps begins between 10-12 years of age, and colectomy is typically performed after the development of adenomas.

Assessment & Evaluation of Genetic Risk

With improvements in technology, the cost to sequence a gene has rapidly decreased. This has led to the introduction of multi-gene panels. For what it previously cost to sequence just *BRCA1* and *BRCA2*, many laboratories are performing analysis of 20-40 genes at once. This new approach increases clinical sensitivity (identifies more mutation carriers), but increases the likelihood of identifying genetic changes of uncertain clinical significance or mutations for which appropriate medical management guidelines do not exist. For this reason, it is essential that the benefits, limitations and risks of genetic testing be discussed with a knowledgeable professional.

When a family or individual presents with a history that indicates a potential inherited cancer syndrome, genetic counseling is strongly recommended. There may be social, financial and emotional consequences to pursuing definitive genetic testing. In order to locate a genetics professional in your area, see http://www.nsgc.org/

Thought Questions

1. A 42 year old woman discovers she has a 1 cm breast lump that is cancerous. Standard surgical options can include lumpectomy (removing only the tumor and preserving the breast) or mastectomy (removing the entire breast). She asks to be tested for the presence of a mutation in *BRCA1* or *BRCA2*. How might the results of the test affect her choice of surgery?

   Your answer:

   Expert Answer

2. What are the advantages to a patient of knowing members of their family carry a familial cancer syndrome gene?

   Your answer:

   Expert Answer

3. What are the disadvantages to a patient of knowing members of their family carry a familial cancer syndrome gene?

   Your answer:

   Expert Answer

4. Why would a physician want to know if a patient carries a familial cancer syndrome gene?

   Your answer:

   Expert Answer

5. Why would a patient from an affected family want to know (or not know) if they personally carry a familial cancer syndrome gene?

   Your answer:

   Expert Answer

Glossary

Autosomal- Relating to any chromosome that is not a sex (X or Y) chromosome

Germline- relating to sperm or egg cells, germline changes when inherited are found every cell of the body

Hit- Mutation

Inherited cancer- occur as part of a cancer predisposition syndrome

Knudson's two-hit hypothesis- The concept that mutations (hits) in two alleles are necessary for inactivation of a tumor suppressor gene

Somatic- relating to specific cells of the body (such as breast cells or colon cells), somatic changes are not passed on to children

Sporadic cancer- occur due to accumulated somatic genetic changes, over time, typically later in life

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