What you should know about Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is a rare genetic condition characterized by multiple, usually early onset, cancers. The most common cancers in LFS include female breast cancer, central nervous system (CNS) cancer, sarcoma (soft tissue and bone cancers), and adrenocortical carcinoma. Individuals with LFS have an increased risk to develop cancers at young ages and multiple primary cancers. LFS is due to a mutation in the TP53 gene.

Cancer Risks and Features Associated with Li-Fraumeni syndrome

Although the most common types of cancers diagnosed in individuals with LFS include early-onset breast cancer, sarcoma, CNS tumors and adrenocortical carcinoma, a wide spectrum of cancer types can occur. Other cancers reported with LFS include leukemia, lymphoma, gastrointestinal (colon, gastric, pancreas), lung, ovarian, and prostate cancer, among several others.

The incidence of cancer in individuals with LFS varies depending on age. Soft tissue sarcomas (most commonly rhabdomyosarcoma) and adrenocortical carcinoma are often seen in early childhood. Bone sarcomas are frequently seen in the teenage years, and breast cancer and brain tumors are commonly seen in early adulthood. Women tend to have higher lifetime risks than men for cancer due to their significantly increased risk for breast cancer. The lifetime risk for cancer in individuals with LFS is ≥70% for men and ≥90% for women. Individuals with LFS are also at risk for developing more than one cancer; studies have shown that people with LFS have a 40%-49% risk to develop a second primary cancer.

<table>
<thead>
<tr>
<th>Risk of Any Cancer:</th>
<th>General Population Risk</th>
<th>LFS Risk Males</th>
<th>LFS Risk Females</th>
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<tbody>
<tr>
<td>By age 30 (females)</td>
<td>1%</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>By age 46 (males)</td>
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<tr>
<td>Lifetime risk</td>
<td>41%</td>
<td>70%</td>
<td>90%</td>
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Genetics and Inheritance of Li-Fraumeni syndrome

Genes are our body’s instructions. They provide our body with information about how to grow and develop. When there is a mutation in a gene, it can cause the gene to no longer function correctly. Each person has two copies of every gene. One copy is inherited from their mother and the other copy is inherited from their father.

LFS is due to a mutation in the TP53 gene. Cancer risks associated with LFS are inherited in an autosomal dominant manner. This means that children, siblings and parents of individuals with a TP53 mutation have a 50% (1 in 2) chance of having the mutation as well. Both males and females can inherit a TP53 mutation and can pass it on to their children.

Most people with LFS inherit the condition from one of their parents who has a mutation in the TP53 gene. However, up to 20% of the time, an individual with LFS is the first person in the family to have the condition.

Sometimes genetic testing may identify a TP53 mutation in only a proportion of cells. This is referred to as mosaicism, and results from a person acquiring a TP53 mutation. These acquired changes may occur during embryological development (before birth), in adulthood due to a phenomenon referred to as clonal hematopoiesis of indeterminate potential (CHIP), among other possibilities. Cancer risks vary significantly based on the cause of mosaicism (i.e. CHIP v. a mutation acquired during development). If mosaicism is identified, additional testing may be recommended.
Managing Cancer Risks
The National Comprehensive Cancer Network (NCCN) provides regularly updated guidelines for management of cancer risk in individuals with LFS. The American Association for Cancer Research (AACR) has also proposed surveillance protocols for LFS. Whenever possible, individuals with LFS should seek management with physicians or centers who are experienced with this condition. Surveillance may include the following:

**Pediatric Risk Management:**
- General Assessment: Complete physical examination every 3–4 months, including blood pressure
- Adrenocortical carcinoma: Ultrasound of abdomen and pelvis every 3-4 months
- Brain tumor: Annual brain MRI
- Sarcoma: Annual whole-body MRI

**Adult Risk Management:**
- General assessment: Complete physical exam, including neurological exam, every 6-12 months; additional surveillance based on family history of cancer
- Brain tumor: Annual brain MRI (as part of whole-body MRI or as separate exam)
- Sarcoma: Annual whole-body MRI
- Melanoma: Annual dermatological exam starting at age 18
- Gastrointestinal Cancer: Colonoscopy and upper endoscopy every 2-5 years starting at age 25
- Breast Cancer: Breast awareness starting at age 18; clinical breast exam every 6-12 months starting at age 20; annual breast MRI between age 20-29; annual mammogram with consideration of tomosynthesis alternating with annual breast MRI screening from age 30-75; discuss option of prophylactic risk-reducing mastectomy

Individuals with LFS should avoid or minimize exposure to radiation whenever possible.

**When to Consider Evaluation for Li-Fraumeni syndrome**
- A relative with a TP53 gene mutation
- An individual with a personal history of adrenocortical carcinoma (ACC) or rhabdomyosarcoma
- A woman with early-onset breast cancer
- A child with hypodiploid acute lymphoblastic leukemia diagnosed < age 21
- An individual with a tumor belonging to the LFS tumor spectrum and family history of LFS tumors
- An individual with multiple tumors (two of which belong to the LFS tumor spectrum)

**Genetic Counseling**
In many families, the cancer history may be due to a combination of genetic and environmental factors. In addition, other genetic conditions (i.e. other gene mutations) may appear clinically similar to LFS. For this reason, a detailed review of the family history by a genetics professional is important before pursuing genetic testing. A genetic counselor can help determine which, if any, genetic tests may be helpful for a family and review the benefits, risks and limitations of genetic testing.

Genetic test results can be complicated and are most useful when interpreted by a genetics professional in the context of an individual's personal and family history. To locate a genetic counselor near you, please visit www.nsgc.org and click on the 'Find a Genetic Counselor' link.
Genetic Discrimination

The Genetic Information Nondiscrimination Act (GINA) was signed into federal law in 2008. GINA prohibits health insurers and most employers from discriminating against individuals based on genetic information (including the results of genetic tests and family history information). According to GINA, health insurance companies cannot consider genetic information to be a preexisting condition, nor can they use it to make decisions regarding coverage or rates. GINA also makes it illegal for most employers to use genetic information in making decisions about hiring, firing, promotion, or terms of employment. It is important to note that GINA does not offer protections for life insurance, disability insurance, or long-term care insurance. More information about GINA can be found by contacting a local genetic counselor or by visiting www.ginahelp.org.

Resources

- Li-Fraumeni Syndrome Association - http://www.lfsassociation.org/
- Facing Our Risk of Cancer Empowered - https://www.facingourrisk.org/

References

- Malkin D. Li-fraumeni syndrome. Genes Cancer. 201;2(4):475-84