UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

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Li-Fraumeni Syndrome (*TP53* mutations)

What You Should Know About Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare condition caused by mutations in the *TP53* gene. Individuals with Li-Fraumeni Syndrome (LFS) are at increased risk for several different cancers including breast cancer, brain cancer, blood or hematological cancers, sarcomas, and tumors of the adrenal gland (adrenocortical carcinoma).

Cancer Risks Associated with Li-Fraumeni Syndrome (*TP53* mutations)

Individuals with LFS have an 85-90% chance of developing cancer in their lifetime. A person with LFS who has had cancer has an approximate 15% chance of developing a second cancer, a 4% chance of developing a third cancer, and a 2% chance of developing a fourth cancer. The risk of developing cancer by the age of 40 is 50%.

Cancers associated with LFS include female breast cancer (median age of diagnosis is 33 years), sarcomas of the soft tissue and bone (median age of diagnosis is 14-15 years), brain tumors (median age of diagnosis is 16 years), adrenocortical carcinomas (median age of diagnosis is 3 years). LFS can also be associated with colorectal cancer, endometrial cancer, esophageal cancer, gonadal germ cell tumor, hematopoietic malignancies, lung cancer, melanoma and non-melanoma skin cancer, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, stomach cancer, thyroid cancer, and renal cancer.

Risks to Family Members

Mutations in the *TP53* gene are inherited in an autosomal dominant fashion. This means that children, brothers, sisters, and parents of individuals with a *TP53* mutation have a 1 in 2 (50%) chance of having the mutation as well. Individuals with a *TP53* mutation may develop one cancer, more than one cancer, or none at all. Both males and females can inherit a familial *TP53* mutation and can pass that it on to their children.

Managing the Risks

There are currently no nationally recommended surveillance guidelines for many of the cancers associated with LFS, but several organizations have proposed surveillance protocols for LFS, including the National Comprehensive Cancer Network and the American Association for Cancer Research (AACR). It is important that parents of children with LFS and adults with LFS be on the lookout for any lumps, bumps, bone pain, or signs of illness that cannot otherwise be explained. Individuals should be evaluated promptly by their doctors if such signs develop, as these could be evidence of an underlying cancer.

Pediatric Risk Management (birth to 18 years)

- *General assessment:* Complete physical examination every 3–4 months, including blood pressure, anthropometric measurements plotted on a growth curve

- *Adrenocortical Carcinoma:* Ultrasound of abdomen and pelvis every 3-4 months. In case of unsatisfactory ultrasound, blood tests, may be performed every 3–4 months including: total testosterone, dehydroepiandrosterone sulfate, andandrostenedione

- *Brain Tumor:* Annual brain MRI I (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality).
- *Soft Tissue and Bone Sarcoma:* Annual whole-body MRI

Adult Risk Management

- *General assessment:* Complete physical exam, including neurological exam, every 6-12 months; consider additional surveillance based on the family history of cancer
- *Brain Tumor:* Annual brain MRI (as part of whole body MRI or separate exam).
- *Breast Cancer*
    - Breast awareness (being familiar with ones breasts, with periodic, consistent breast self-exams, reporting any unusual findings to a physician promptly) beginning at age 18.
    - Clinical breast exam every 6-12 months starting at age 20 or at the age of the earliest diagnosed breast cancer in the family if below 20 years of age.
    - Annual breast MRI screening with contrast starting at age 20-29 (or at the age of the earliest diagnosed breast cancer in the family if below 20 years of age); mammogram with consideration of tomosynthesis if MRI is unavailable.
    - Annual mammogram with consideration of tomosynthesis alternating with annual breast MRI screening (such that a breast MRI or mammogram occurs every 6 months) from age 30-75.
    - Management should be considered on an individual basis after age 75.
    - Discuss option of prophylactic risk-reducing mastectomy.
- *Soft Tissue and Bone Sarcoma:*
    - Annual whole-body MRI (if unavailable then can consider clinical trial to screen for cancer or consider alternate comprehensive imaging methods).
    - Ultrasound of abdomen and pelvis every 12 months.
- *Melanoma:* Annual dermatological examination starting at 18 years old.
- *Gastrointestinal cancer*: Colonoscopy and upper endoscopy every 2-5 years starting at age 25 or 5 years before the earliest known colon cancer in the family, whichever comes first.

Agents/Circumstances to Avoid

Individuals with LFS should avoid or minimize exposure to radiation whenever possible. Individuals with LFS are also encouraged to avoid or minimize exposures to other known carcinogens (e.g. smoking and secondhand smoke). Additionally, they are encouraged to avoid excess sun exposure and always use sun protective strategies when outdoors in the sunlight.

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