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Li-Fraumeni Syndrome : Current Strategies and Future Perspectives

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Li-Fraumeni syndrome (LFS) is a rare inherited cancer predisposition syndrome caused by germline mutations in the *TP53* tumor suppressor gene. It predisposes affected individuals to a wide spectrum of early-onset malignancies, including sarcomas, breast cancer, brain tumors, and adrenocortical carcinoma. Advances in genetic testing and risk management strategies have enhanced the identification and clinical management of LFS patients. Comprehensive surveillance has demonstrated increased survival rates through proactive screening. Beyond surveillance, research is exploring novel approaches such as liquid biopsy for early cancer detection and chemoprevention strategies, including metformin trials, to mitigate cancer risk. This review discusses the molecular basis, clinical spectrum, surveillance strategies, and emerging research in LFS.

Key Words : Li-Fraumeni syndrome · Cancer predisposition syndrome · Cancer surveillance.

INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare, inherited cancer predisposition syndrome first described in 1969 by Frederick Li and Joseph Fraumeni[9,10]. They reported multiple families in which children developed rhabdomyosarcomas and close relatives developed diverse early-onset malignancies at frequencies far exceeding chance. This observation suggested a previously unrecognized familial cancer syndrome with autosomal dominant inheritance. Decades later, in 1990, Malkin et al.[14] identified germline mutations in the *TP53* tumor-suppressor gene as the underlying genetic cause of LFS. LFS is thus named after its discoverers and is often considered the prototypical hereditary cancer syndrome caused by *TP53* mutations.

The diagnosis of LFS has been based on well-established clinical criteria that have evolved over time. The classical definition, established in 1988 by Li and Fraumeni, primarily relies on family history and specific cancer types occurring at young ages[11]. These criteria have been used to identify families with a high likelihood of harboring germline *TP53* mutations. However, a subset of patients-especially in the pediatric group-have been diagnosed as *TP53* mutation carriers even without a notable family history of cancer. The classic criteria are considered too restrictive, potentially missing a significant number of mutation carriers. Over the years, revised criteria, such as the Chompret criteria, have been introduced to capture a broader

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Table 1. Clinical criteria for identification of Li-Fraumeni syndrome

Criteria	Definition
Classical LFS criteria (1988)	All of the following : 1) sarcoma <45 years; 2) first-degree relative with any cancer <45 years; and 3) another first- or second-degree relative with sarcoma at any age or cancer <45 years
Chompret criteria (2015)	One of the following : 1) familial presentation : LFS spectrum tumor <46 years + relative with LFS tumor (except breast cancer if proband has breast cancer) <56 years or multiple tumors; 2) multiple primary tumors : at least two LFS spectrum tumors before 46 years of age; 3) rare tumors : adrenocortical carcinoma, choroid plexus carcinoma, embryonal anaplastic rhabdomyosarcoma, regardless of family history; and 4) early-onset breast cancer : breast cancer before 31 years

LFS spectrum tumors : adrenocortical carcinomas, breast cancers, central nervous system tumors, osteosarcomas, and soft tissue sarcomas. LFS : Li-Fraumeni syndrome

range of affected individuals (Table 1)[1]. This revised criteria has significantly improved the identification of individuals at risk for LFS, especially those without a strong familial cancer history. The Chompret criteria are now widely used in clinical practice and recommended for genetic counseling and *TP53* testing in suspected LFS cases.

TP53 MUTATIONS AND CANCER SUSCEPTIBILITY

LFS is caused by inherited pathogenic variants in *TP53*, located on chromosome 17p13.1, which encodes the p53 protein. *TP53* plays a pivotal role in preserving genomic stability by regulating DNA repair, cell-cycle arrest, and apoptosis in response to DNA damage. It is often called the "guardian of the genome," and somatic *TP53* mutations are found in over half of all sporadic human cancers[16]. In LFS, a germline *TP53* mutation is present from birth, severely compromising p53's tumor-suppressor function across all cells. This confers an extreme susceptibility to cancers : affected individuals have an estimated approximately 70% lifetime risk of cancer in men and ~90% in women[21], with many developing multiple primary cancers over their lifetime[13]. Notably, LFS patients have an increased risk for early-onset malignancies and an 83-fold increased risk to develop multiple primary cancers[8,15].

Ongoing research suggests that additional modifiers and co-operating genetic factors may influence cancer risk in LFS. For example, intragenic *TP53* polymorphisms, mutations in other p53 pathway genes, telomere attrition, and other genetic modifiers can affect the age of onset and tumor spectrum in *TP53* mutation carriers[7,17-19]. These findings highlight that the *TP53* mutation establishes the baseline risk of tumor development in LFS, but other genetic or environmental factors modulate the phenotype, contributing to variability in cancer types and timing among affected individuals.

CLINICAL SPECTRUM OF CANCERS IN LFS

One hallmark of LFS is its remarkably broad spectrum of malignancies, often occurring at young ages. The frequencies of tumors frequently observed in patients with LFS are illustrated in Fig. 1. Five cancer types account for the majority of LFS tumors : adrenocortical carcinomas (ACCs), breast cancers, central nervous system tumors, osteosarcomas, and soft tissue sarcomas (STSs)[4]. In children and adolescents with LFS, osteosarcoma is the most common tumor (30%), followed by ACC (27%), brain tumors (25%), and STS (23%)[8]. Breast cancer is the most frequently encountered malignancy (79% of women), followed by STS (27%) in adults with LFS[8]. Brain tumors occur in approximately 25% of LFS patients and are one of the most frequently diagnosed malignancies, especially in children[8]. The cumulative lifetime risk of developing a brain tumor in LFS patients is estimated to be 6% in females and 19% in males. LFS patients develop a range of brain tumors, including high-grade gliomas, ependymoma, medulloblastomas, and the characteristic choroid plexus carcinoma.

In addition to these core cancers, individuals with LFS are at risk for many other malignancies. Leukemia (particularly acute leukemias in childhood), early-onset colorectal and gastric carcinomas, lung cancer (in non-smokers at young ages), melanoma, head and neck cancers in children, pancreatic cancer, prostate cancer, and others have all been reported at higher rates in LFS patients[5]. Importantly, cancer survivors with LFS remain at risk for multiple subsequent primary cancers, including therapy-related malignancies. It is not uncommon for a patient with LFS to develop two, three, or more independent cancers in

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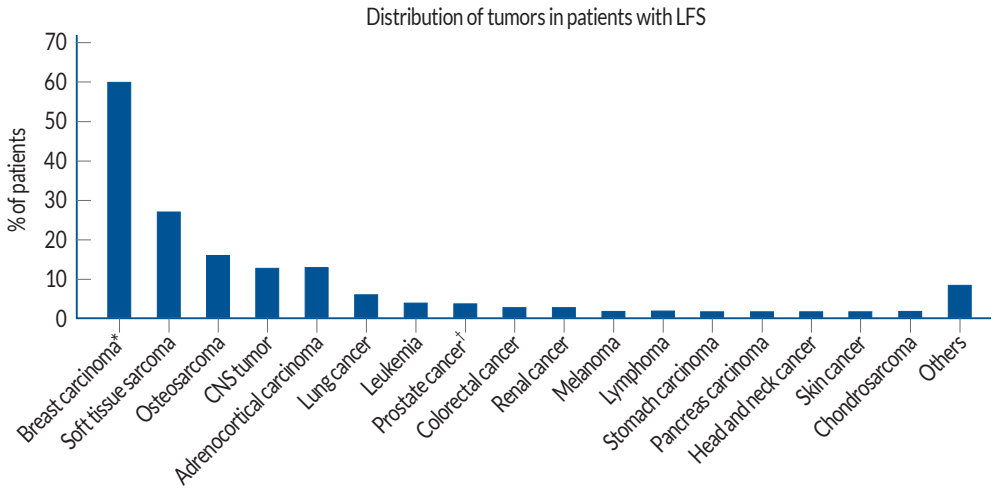

Fig. 1. Distribution of tumors in LFS patients[1]. The frequencies of tumors frequently observed in patients with LFS are presented. *In females, †in males. LFS : Li-Fraumeni syndrome, CNS : central nervous system.

Table 2. Surveillance guidelines summary

Age group	Surveillance modality	Frequency
Birth to 18 years	Physical examination (focus on endocrine and neurologic signs)	Every 3–4 months
	Whole-body MRI (including head-to-toe imaging)	Annually
	Brain MRI (with gadolinium contrast for first scan, then optional contrast for follow-ups)	Annually
	Abdominal and pelvic ultrasound (for ACC screening)	Every 3–4 months
	Blood tests (total testosterone, DHEAS, androstenedione, CBC, LDH)	Every 3–4 months
Adults (≥18 years)	Physical examination	Every 6 months
	Whole-body MRI	Annually
	Brain MRI	Annually (until age 50)
	Breast MRI (for women aged 20–75 years)	Annually (alternating with WBMRI every 6 months)
	Upper endoscopy and colonoscopy (for gastrointestinal cancer screening)	Every 2–5 years (starting at age 25)
	Dermatological examination (for melanoma risk)	Annually
	Risk-reducing mastectomy (for women with *TP53* mutations)	Considered case-by-case

MRI : magnetic resonance imaging, ACC : adrenocortical carcinoma, DHEAS : dehydroepiandrosterone-sulfate, CBC : complete blood count, LDH : lactate dehydrogenase, WBMRI : whole-body MRI

their lifetime[12]. These cancers tend to occur decades earlier than sporadic cases of the same tumor types[13].

CLINICAL MANAGEMENT INCLUDING CANCER SURVEILLANCE

Clinical management of LFS patients focuses on cancer surveillance and early detection. Specialized surveillance protocols have been developed internationally. The first comprehensive surveillance protocol (Toronto protocol) was reported in 2011 using frequent physical examination, whole-body magnetic resonance imaging (MRI), and ultrasound as well as mammograms and colonoscopies for adults at regular, frequent intervals[23]. Building on this, multiple expert groups (e.g., the American Association for Cancer Research, UK Cancer Genetics Group, and NCCN) have published guidelines that largely align with the Toronto approach, and a consensus guideline was developed in 2017[2,8,15,22]. The general approach is to begin screening from infancy and continue lifelong, with frequent clinical exams and regular whole-body imaging. The consensus guideline is summarized in Table 2. In Korea, there are practical

challenges in implementing the guideline due to limitations in insurance coverage, and efforts are needed to address this issue.

This proactive surveillance strategy is burdensome but has shown clear clinical benefit. A landmark study by Villani et al.[23], which included both children and adults, demonstrated that *TP53* mutation carriers who followed an intensive surveillance protocol had dramatically improved outcomes : a 3-year overall survival of 100% in the surveillance group, compared to only 21% in a comparable non-surveillance group. Tumors detected under surveillance were often found at an asymptomatic, early stage – for instance, small high-grade tumors that were curable – whereas unscreened individuals often presented with advanced, symptomatic cancers. A subsequent study with a larger patient cohort and longer follow-up duration confirmed sustained survival benefits from ongoing screening, reporting a 5-year overall survival rate of 88.8% in the surveillance group compared to 59.6% in the non-surveillance group[22]. These findings have made early detection a cornerstone of LFS management.

Beyond the surveillance, there are general principles in treating LFS patients. When an LFS patient is diagnosed with cancer, standard oncologic treatment is often indicated, but certain modifications are recommended due to the risk of secondary cancers. Because radiation exposure can precipitate second primary cancers in *TP53* mutation carriers, clinicians aim to avoid or minimize radiation therapy whenever possible[20]. For example, women with LFS who develop breast cancer are usually advised to undergo bilateral mastectomy over breast-conserving surgery, not only to reduce the risk of a second breast cancer but also to avoid the need for therapeutic radiation to the breast. Similarly, neurosurgeons treating a brain tumor in an LFS patient might pursue maximal safe resection to potentially avoid radiation, and radiation oncologists may use the lowest effective dose or advanced techniques to limit exposure. Lifestyle modifications are also advised : patients are counseled to avoid known carcinogens – for example, refraining from tobacco and excessive sun exposure, limiting alcohol, and minimizing unnecessary diagnostic radiation like computed tomography scans.

EMERGING RESEARCH AND FUTURE DIRECTIONS

Despite significant advances in understanding and managing LFS, ongoing research is actively addressing the remaining gaps and testing innovative strategies to further improve outcomes. One strategy is the incorporation of early-detection technologies like liquid biopsy into LFS surveillance. Traditional imaging-based screening has limitations in sensitivity and timing, but recent studies show that analyzing circulating tumor DNA can detect malignancies even earlier than imaging in LFS patients[25]. For example, a study demonstrated that a multi-modal liquid biopsy assay could detect cancer-associated signals in the blood of *TP53* carriers before tumors were visible on scans, with a high negative predictive value. If validated in larger trials, integrating blood-based biomarkers or genomic assays could complement existing surveillance, allowing less frequent imaging or earlier diagnosis.

Another critical area of research is chemoprevention – finding medications to reduce the incidence of new cancers in LFS. Currently, there are no approved drugs to mitigate risk, but a growing body of evidence suggests some agents might have protective effects. One of the most anticipated interventions is metformin, a well-known anti-diabetic drug. Preclinical models of LFS (including *TP53*-mutant mice) have hinted that metformin may delay tumor onset, potentially by normalizing metabolic abnormalities associated with mutant p53[24]. LFS patients often show elevated mitochondrial oxidative metabolism, and metformin's ability to dampen mitochondrial respiration provides a biological rationale for its use[24]. These insights have led to international collaborative efforts and clinical trials to test metformin in *TP53* mutation carriers. Notably, the Metformin in Li-Fraumeni Syndrome (MILI) trial is a randomized study investigating whether metformin can reduce cancer incidence or prolong cancer-free survival in adults with LFS who are under active MRI surveillance[3]. Consideration for expansion of a pediatric cohort is also being actively explored[6]. Results from such trials in the coming years will clarify if metformin (or other metabolic modulators) can become a preventive therapy in LFS.

On the genetic front, future directions include refining risk prediction and possibly gene-specific interventions. As more LFS families are studied, genotype-phenotype patterns may allow better risk stratification, which could eventually inform personalized surveillance intensity. Moreover, advanced genomic techniques are searching for additional predisposition genes in those LFS-like families without *TP53* mutations. While *TP53* remains the main player, discovering other rare variants (in genes involved in DNA damage response, cell cycle,

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or telomere maintenance) could expand our understanding of hereditary cancer biology and identify new targets for intervention[13].

CONCLUSION

LFS remains one of the most challenging hereditary cancer syndromes due to its high penetrance and diverse tumor spectrum. While advancements in genetic testing and surveillance strategies have substantially improved early detection and survival, ongoing research is essential to optimize patient care. Novel approaches such as liquid biopsy, chemoprevention with metformin, and precision-based risk stratification hold promise for reducing cancer burden in affected individuals. Future studies will further refine risk prediction, develop targeted interventions, and enhance long-term survivorship strategies for individuals with LFS.

AUTHOR'S DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

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