Journal of Clinical and Medical Images[R] ISSN 2640-9015 | Volume 9

Review Article Open Access

A Review of the Decision Process for Risk-Reducing Mastectomy in Adolescents and Young Adults with Li-Fraumeni Syndrome

Çigdem Berk Ozcan*

Selcuk University Aksehir Kadir Yallagoz Health College Nursing Department Konya, Turkey

***Corresponding author:**

Çigdem Berk Ozcan,
Selcuk University Aksehir Kadir Yallagoz Health College Nursing Department Konya, Turkey

Received: 28 Nov 2025
Accepted: 01 Oct 2025
Published: 07 Oct 2025
J Short Name: ACMCR

Keywords:

Li-Fraumeni Syndrome; Risk-Reducing Mastectomy; Breast Cancer

Citation:

Çigdem Berk Ozcan, A Review of the Decision Process for Risk-Reducing Mastectomy in Adolescents and Young Adults with Li-Fraumeni Syndrome. Jour of Clin and Medi Images® 2025; V9(1): 1-8

1. Abstract

1.1. Objective

Li-Fraumeni Syndrome is a rare cancer predisposition syndrome caused by autosomal dominant germline mutations in the TP53 gene. LFS is characterized by high lifetime cancer risk, high risk of multiple primary cancers, early cancer onset, and a broad spectrum of cancers. Individuals with Li-Fraumeni Syndrome are at risk of breast cancer at a much earlier age than the general population, with a mean age of onset around 32 years. Materials and Methods: Management of breast cancer risk in this population includes prophylactic bilateral mastectomy. Electronic databases, including PubMed, Cochrane Library, Scopus, Ovid and WOS, were searched from 2015 to 2025. Search terms were "Li-Fraumeni syndrome", "risk-reducing mastectomy", and "breast cancer". English-language articles published in peer-reviewed journals and guideline recommendations were included in the review. The decision to undergo risk-reducing mastectomy surgery in women who have not been diagnosed with breast cancer but have a genetic predisposition and are known to be at very high risk of developing the disease is summarized. Results: Accurately determining the risk of breast cancer is vital, considering mutations in predisposing genes. This study provides evidence of risk-reducing mastectomy and surgical decision-making in adolescents and young adults with Li-Fraumeni syndrome. Conclusion: In mastectomy surgeries that reduce risk, a comprehensive and personalized approach to the surgical process, as well as patient selection and management for multidisciplinary intervention, are of great importance.

2. Introduction

2.1. Li-Fraumeni Syndrome

Li-Fraumeni Syndrome (LFS) is a cancer predisposition syndrome caused by autosomal dominant germline mutations in the TP53 gene. LFS is characterized by a high lifetime risk of cancer, including multiple primary cancers and a wide range of associated cancers. Classic LFS cancers include brain, breast, sarcoma, and adrenal gland [1]. The syndrome is rare, and the frequency of TP53 mutation carriers is estimated to be between 1/5,000 and 1/20,000. However, it is thought that the disease is underdiagnosed worldwide [2,3]. Li-Fraumeni syndrome was first described in 1969 by Dr. Frederick Li and Dr. Joseph Fraumeni [4]. (4) First described more than fifty years ago by Frederick P. Li and Joseph F. Fraumeni, the initial suspicion was raised by the observation of an "increased familial susceptibility to cancer" and the consideration of a potential familial origin for malignancies observed "not only by the large number of individuals affected but also by the excessive occurrence of multiple primary neoplasms." [4,5]. The diagnosis of LFS is difficult due to its heterogeneous clinical presentation and diagnostic inconsistencies.6,7 Furthermore, monitoring LFS patients poses additional challenges for clinicians, as individuals often face recurrent malignancies due to genetic predisposition or complications from previous cancer treatments. The TP53 gene in cells encodes tumor protein 53, which plays a crucial role in tumor suppression and cell death [8,9]. The TP53 pathway is activated by cellular stress, including oncogene expression, DNA damage, low oxygen levels, metabolic dysfunction, and replication errors [10]. TP53 is a tumor suppressor gene located on chromosome 17. TP53's role in tumor suppression has earned it the nickname "guardian of the genome." It has been shown that cells lacking normal TP53 function continue to divide and multiply indiscriminately, leading to malignant tumors. In mice with loss-of-function mutations, it was observed that 100% of mice developed tumors within nine months after complete elimination of TP53 [10]. TP53 is a critical tumor suppressor that plays a role in regulating cell cycle progression, DNA repair, apoptosis, and

aging. The coding and alterations of the suppressor p53 protein commonly contribute to cancer development [11,12]. In individuals with LFS, germline mutations cause all cells in their bodies to have only one functional copy of the TP53 gene.

Geographically, LFS is distributed globally, with no clear ethnic or racial predilections. However, certain populations exhibit high prevalence rates due to mutations attributable to genetic drift, population disruptions, or inbreeding [13]. Although rare, LFS shows significant variability in its penetration rate, along with interindividual variability in tumor spectrum, age of onset, and disease course, and this variability is attributed to genes, environmental effects, and random events [14-17]. It is suggested that LFS familial syndrome carries a high risk of cancer at a rate of approximately 80% throughout an individual's lifetime [18]. Studies estimate that germline TP53 mutations are present in more than 350,000 individuals. This indicates that the number of cases is significantly higher than the number of registered cases and that LFS cases worldwide are potentially underdiagnosed [19,20]. However, if the criteria are not met, testing for other hereditary syndromes should be considered. Between 50-70% of individuals defined by the classic LFS criteria test positive for a variant in the TP53 gene [21]. According to the National Comprehensive Cancer Network (NCCN) guidelines (2024), it is estimated that these diagnostic criteria have a high positive predictive value when confirmed by molecular testing [22]. It is indicated if the individual comes from a family with a known TP53 variant and meets the classic criteria for LFS, has a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia, has somatic tumor testing showing an allele frequency greater than 50% for the TP53 pathogenic variant or decreased p53 staining by immunohistochemistry, and meets one measure of the Chompret criteria [21].

3. Materials and Methods

This study searched electronic databases including PubMed, Cochrane Library, Scopus, Ovid, and WOS between 2015 and 2025. All articles were searched using the English keywords "Li-Fraumeni syndrome," "risk-reducing mastectomy," and "breast cancer." Additionally, relevant sources were accessed through Google Scholar. The review included articles written in English and published in peer-reviewed journals, as well as guideline recommendations.

4. Findings

4.1. Diagnosis of Li-Fraumeni Syndrome

Before the discovery of the TP53 mutation behind LFS, clinicians needed a way to identify individuals and families with this disease. In 1988, Dr. Li and Dr. Fraumeni established the classic diagnostic criteria for LFS based on a study of 24 families with cancers that fit the Li-Fraumeni phenotype (Table 1). The classic criteria for LFS are [23,24].

It is currently estimated that between 7% and 20% of first-time germline mutations occur during gametogenesis or embryogenesis.23 It requires the individual to meet one of the Chompret diagnostic criteria [21,25,26]. When classical LFS and Chompret criteria are combined, molecular test sensitivity is reported to be 95% [27].

Table 1: Diagnostic criteria for Li-Fraumeni syndrome requiring further screening for TP53 mutation in Hereditary Mutations

Diagnostic Criteria	Definition
Classical Criteria	Presence of all of the following: - Sarcoma diagnosed at <45 years of age, - First-degree relative <45 years of age with any type of cancer, - First/second-degree relative with sarcoma at any age or any cancer under 45 years of age,
Chompret Criteria (updated)	Presence of one of the following: - Tumor from the Li-Fraumeni spectrum (sarcoma, breast cancer, central nervous system tumor, adrenocortical carcinoma, leukemia or lung cancer) <46 years and at least one first/second-degree relative with a Li-Fraumeni tumor (excluding breast cancer if the proband has breast cancer) <56 years or multiple tumors; - Multiple tumors (excluding multiple breast tumors), two of which belong to the Li-Fraumeni spectrum, the first of which occurs at <46 years of age, - Diagnosis of embryonal anaplastic subtype adrenocortical carcinoma, choroid plexus tumor or rhabdomyosarcoma, regardless of age and family history - Breast cancer <31

4.2. Clinical Features of Li-Fraumeni Syndrome

Li-Fraumeni Syndrome is characterized by an increased risk of cancer in childhood and adulthood. Men with LFS are 151 times more likely to develop cancer than the general population and women with LFS are 1,085 times more likely to develop cancer than the general population; they are also 7.1 times more likely to develop cancer than men with LFS, largely due to the risk of breast cancer [28]. In fact, breast cancer is the most common cancer in female patients with LFS [29]. Previous studies have shown that women with LFS develop breast cancer almost three decades earlier than the general population and that the average age of onset is usually around 32-38 years. 29–32 Studies have drawn attention to the potential impact of reproductive factors, as significant protective effects of breastfeeding for longer than seven months have been observed in relevant populations [33]. Breast cancer in the context of LFS exhibits aggressive histopathologic features, including high histologic grade and overexpression of the HER2/neu oncogene, and tends to have a lower overall survival compared to incidental cases [30,34]. Many cases of LFS breast cancer are estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) positive, suggesting a possible association of early-onset HER2 positive breast cancer with the presence of TP53 mutations [35]. Breast cancer has different clinical manifestations, suggesting that these are early signs and symptoms of LFS. Notably, breast cancers in LFS often occur at a younger age compared to incidental cases, making early breast cancer a worrying sign for clinicians to initiate an in-depth study of LFS [29,36,37]. In a prospective cohort study conducted by Mai et al. to classify the risk of malignancy, soft tissue sarcoma, osteosarcoma and brain cancer were the most common primary cancer diagnoses in individuals with LFS under the age of 18, while breast cancer was the most common diagnosis in individuals between the ages of 18 and 44. They found that soft tissue sarcoma was the most common diagnosis at the age of 45 years. They also found that the cumulative cancer risk reaches 50% by age 31 for women and 46 for men, and approaches 100% for both sexes by age 70. Breast cancer was the second most common cancer diagnosis.38 Breast cancer is the most common cancer in women with LFS, with an incidence risk of 49% by age 60 and a lifetime risk of 85% [38,39]. Women with TP53 mutation diagnosed with breast cancer tend to be hormone receptor and HER-2 positive, ductal, high stage and invasive. They found that the average age at diagnosis was between 32 and 33 years and that women with LFS were more likely to be diagnosed with multiple primary breast cancers than the general population [30,40]. The clinical manifestations of breast cancer are diverse, and the possibility of early emerging signs and symptoms of LFS needs to be carefully examined. Of particular concern is the observation that breast cancers in LFS frequently manifest at a younger age compared to incidental cases, underscoring the importance of early breast cancer detection as a crucial clinical indicator for initiating a comprehensive study of LFS [29,36,37].

4.3. Management and Follow-up of Li-Fraumeni Syndrome

The follow-up protocol encompasses a comprehensive physical examination, along with whole body magnetic resonance imaging (MRI), brain MRI, breast MRI, mammography, abdominal and pelvic ultrasonography, and colonoscopy. In the screening and follow-up study conducted by Villani et al., the 5-year survival rates were 89% in the follow-up group that accepted screening and 60% in the group that did not accept screening [41]. These results demonstrate the feasibility and benefit of comprehensive screening for individuals with LFS. The Toronto protocol and the NCCN recommend the use of MRI in place of other cancer screenings, such as mammography or positron emission tomography (PET) scans. Individuals with LFS should avoid radiation as much as possible due to the risk of "subsequent secondary malignancies" [42]. The National Cancer Institute has made multiple references to risk-reducing mastectomy (RAM), particularly in the context of breast cancer. It is recommended that individuals undergo counseling to discuss the degree of protection, reconstruction options, risks, family history, and risk of permanent breast cancer. Given the risk of radiation therapy-induced sarcoma, mastectomy is recommended as the primary treatment for breast cancer in women with LFS, rather than the combination treatment of lumpectomy and radiation recommended for the general population for early-stage breast cancers.43 The latest guidelines recommendations for breast cancer screening are summarized below (Table 2).

Table 2: Current guideline recommendations for breast cancer screening

	From 18 years old	20-25 years old and above	20-75 years old	Mastectomy Preference
Toronto ' Protocol (2016) [41]	From the age of 18 - Breast self-examination, once every month	•20-25 years and older - Clinical breast exam, every 6 months	•20-75 years old - Mammography and breast MRI, once a year	- Risk-reducing bilateral mastectomy should be considered.

NCCN (2024) [42]	From the age of 18 - Breast awareness	• From age 20 onwards - Clinical breast examination, every 6-12 months - Breast screening: • Ages 20-29: If breast MRI is not available before age 20 (if the earliest diagnosed breast cancer in the family was before age 20), mammography (due to concerns about radiation exposure risk in pathogenic/high-risk variant carriers, breast MRI is preferred before age 20, annually) (once a year) • Ages 30-75: Breast MRI + mammography, once a year (MRI: contrast-enhanced and non-contrast)	• >75 years old: Evaluated individually - Breast cancer treatment received and bilateral mastectomy not undergone TP53 Pathogenic/high probability pathogenic variants: Breast MRI + mammography, once a year	- Discuss risk-reducing mastectomy, addressing psychosocial and quality of life aspects - In patients diagnosed with breast cancer, mastectomy should be preferred over lumpectomy/radiation to reduce the risk of radiation-induced sarcoma.
AACR (2017)[24]	From the age of 18 - Breast awareness	• From age 20 onwards - Clinical breast examination, every 6 months	• Ages 20-75 - Breast MRI, once a year	- Risk-reducing bilateral mastectomy should be considered.
GENTURIS (2020)[40]	Ages 18-65 - Breast MRI, once a year	• Ages 18-65 - Breast MRI, once a year	• Ages 18-65 - Breast MRI, once a year	
JOE & AEGH (2020)[44]	From the age of 18 -Clinical breast examination, every 6 months	• Ages 20 to 75 - Breast MRI, once a year	• Ages 20 to 75 - Breast MRI, once a year	
Japanese LFS Expert Group (2021)[45]	From the age of 18 - Breast self-examination	• From age 20 onwards - Clinical breast examination, every 6 m	• Ages 20-75 - Breast MRI, once a year (Breast MRI and abdominal-pelvic ultrasound, alternated with annual whole-body MRI; screening at least every 6 months)	

4.4. Risk-Reducing Mastectomy in Hereditary Cancer Syndromes

A mastectomy, a treatment for breast cancer, involves removing breast tissue after a tumor is detected. A risk-reducing mastectomy is a surgery "performed to reduce the risk of breast cancer in a woman who has not been diagnosed with breast cancer but is known to be at very high risk of the disease" [43,44]. While the efficacy of RAM procedures in reducing the risk of breast cancer in the general population remains to be elucidated, evidence suggests a potential reduction in risk and enhanced oncologic outcomes in high-risk populations [47]. According to the CDC (2024), the prevalence of TP53 mutations, a genetic factor associated with hereditary breast and ovarian cancer, is notably lower than that of BRCA1/2 mutations. Approximately 1 in 500 women in the United States carries a mutation in the BRCA1 or BRCA2 genes.48 Women with a history of breast cancer who carry a mutation in the BRCA1 or BRCA2 gene have indicated the factors that influenced their decision to undergo a risk-reducing mastectomy (RAM). These factors include the fear of developing breast cancer, the desire for psychological reassurance, the intention to extend life expectancy, the aspiration for autonomy, the need for insurance coverage, financial considerations, the perspective of their partner, the influence of their family history, the impact of the "Angelina Jolie Effect," their perception of risk, the influence of siblings, the opinions of physicians, the timing of genetic testing, and the desire to prevent the development of metastatic disease. While women with BRCA1/2 mutations who opted for RAM generally expressed satisfaction, they also reported negative aspects such as distorted body image, unsatisfactory cosmetic results, complications, decreased sexuality, emotional issues, and a lack of education regarding post-RAM follow-up [49-51].

4.5. Risk-Reducing Mastectomy Surgery for Hereditary Cancer Syndromes

A mastectomy, a surgical procedure used to treat breast cancer, involves the removal of breast tissue after a breast tumor has been detected. A risk-reducing mastectomy, on the other hand, is a surgical intervention "performed to reduce the risk of breast cancer in a woman who has not previously been diagnosed with breast cancer but is known to be at very high risk of the disease" [43]. Comeaux et al define risk-reducing mastectomy surgery as an invasive procedure that reduces the risk of breast cancer "for women at high risk of breast cancer."46 While the efficacy of RAM procedures in reducing the risk of breast cancer in the general population remains to be elucidated, there is encouraging evidence from studies conducted on high-risk populations [47]. A plethora of surgical interventions are available for the treatment of RAM. The initial primary classification of surgical interventions involves the removal of one or both breasts. Bilateral risk-reducing mastectomy is a surgical procedure in which both breasts are removed before a diagnosis of breast cancer is established. In the event that a woman is diagnosed with cancer in a single breast, the surgical intervention of contralateral risk-reducing mastectomy is strongly recommended. This procedure entails the prophylactic removal of the contralateral, unaffected breast [43]. A radical mastectomy involves removing all breast tissue, skin, nipples, the chest wall muscles under the breast, and some lymph nodes in the armpit. Radical mastectomy was the standard procedure until the 1970s but is now rarely performed only in cases where the tumor has invaded the chest muscles and has not shrunk with chemotherapy. Today, surgeons generally choose to perform a modified radical mastectomy (removal of breast tissue, skin, and nipples), a skin-sparing mastectomy (removal of breast tissue and nipples), or a nipple-sparing mastectomy (removal of breast tissue and preservation of skin and nipples) [50]. A variety of reconstruction options exists subsequent to RAM. The process of tissue expansion, also known as reconstruction, entails the strategic placement of expanders during the initial mastectomy procedure or subsequent to the mastectomy surgery, followed by a dedicated reconstruction surgery in a separate procedure. Reconstruction may involve the use of implants or autologous tissue, among other options within these categories. Some individuals opt for the "stay straight" approach, which involves avoiding reconstruction [52].

Adolescents and young adults diagnosed with cancer represent a particularly under-researched and under-met segment of oncology patients. According to the NCCN (2024), the term "adolescents and young adults with cancer" is used to denote individuals between the ages of 15 and 39.42 Overall, adolescents and young adults with cancer have unequal access to oncology services, complex psychosocial and financial impacts from a cancer diagnosis, and only modest improved survival compared with those with adult and childhood cancers [53]. Cancer-related syndromes are experienced differently by young adults and adolescents than by older adults. Cancer patients in their teens and early adulthood experience more psychological distress and fear of recurrence than older adults with cancer. In addition, cancer in adolescents and young adults is associated with an increased risk of cardiovascular disease, endocrine dysfunction, neurocognitive impairment, sexual dysfunction and fertility issues. Education, employment, financial difficulties and romantic relationships also complicate the cancer experience for young people [54]. Studies of adolescents and young adults with Li-Fraumeni syndrome and family members' illness narratives have identified the roles of family factors influencing the experience of LFS in adolescents and young adults with cancer. Family history and the information provided by healthcare professionals significantly influence risk perceptions. Another common concern is the impact on relationships and reproductive planning. The impact of hereditary cancer predisposition on self-esteem, sexual function, and body image has been highlighted [55]. A qualitative study discussing the benefits and burdens of risk management for adolescents and young adults with LFS found that individuals were aware of their breast cancer risk and were planning RAM. They also shared concerns about the benefits of RAM, such as controlling their breast cancer risk, but also the physical and emotional burden and impact on romantic relationships and breastfeeding [56].

Research on the RAM decision-making process focuses on women who are carriers of the BRCA1/2 mutation. The cumulative risk of breast cancer for women with the BRCA1/2 mutation is 50% by age 80, and the age of onset is reported to be between 41 and 50 for women with the BRCA1 mutation and 51 and 60 for women with the BRCA2 mutation [57,58]. Approximately 10-15% of diagnosed breast cancers are associated with known hereditary cancer syndromes, and about 60% carry a BRCA1/2 mutation 57, for this reason, it is observed that the majority of the literature on RAM decisions in hereditary cancer syndromes focuses on women with BRCA1/2 mutations. However, women with LFS and BRCA1/2 mutations have a higher lifetime risk of breast cancer, and the age of cancer onset is lower in these women. The implementation of the recommendations found in RAM studies does not adequately reflect the experiences of this population [40]. In a cohort study conducted by Siegel et al. with 205 women with LFS aged between 15 and 73 years, 63% reported having undergone mastectomy. They found that RAM was associated with having children, having previously breastfed, knowing the genetic condition at the time of breast cancer diagnosis, and high cancer anxiety. In this study, they found that women with LFS underwent complete bilateral RAM at a median age of 39, despite the mean age of onset of LFS-related breast cancer being 32 years. They noted that RAM should be considered in women with LFS in their 20s or early 30s to prevent primary breast cancer, but that the decision at this early age is complicated by body image concerns and desires to breastfeed in the future 40 For the importance given to the desire to breastfeed, the impact of RAM on body image and dating is emphasized as an important factor [40,56]. It is important to note that family histo-

ry and family discussions are not equivalent for this population. Despite being open to communication, research has shown that adolescents and young adults with LFS experience complexities in family communication about LFS. These complexities include balancing information sharing with emotional protection and considering the impact on mental health [59]. Research also suggests that individuals with rare disorders like LFS may struggle to find healthcare providers who are familiar with their condition and knowledgeable about care recommendations [60].

5. Conclusion

This study summarizes the preferences of adolescents and young adults with LFS, providing insights into the factors influencing the RAM decision-making process in these groups. Improved survival is often the preferred option for women carrying the p53 genetic mutation. Accurately assessing this risk by considering factors such as the presence of mutations in breast cancer susceptibility genes is crucial. Interest in risk-reducing mastectomy has increased alongside advancements in genetic sequencing techniques, breast reconstruction, and breast imaging, as well as the rise of celebrity prophylactic breast surgery. The decision to perform RAM is based on the interconnected nursing interventions of psychosocial factors, beliefs, and emotions. In the context of this comprehensive decision-making process regarding surgical intervention for patients with associated risks, it is imperative to adopt a multidisciplinary and personalized approach to each patient, ensuring the selection of those who will derive the greatest benefit from this intervention. Complications may include adverse effects on physical, emotional, and sexual health, and potential outcomes associated with the implementation of risk-reducing mastectomy.

References

1. Vogel WH. Li-Fraumeni Syndrome. 2017; 45:742-6.
2. Stoltze U. Clinical characteristics and registry-validated extended pedigrees of germline TP53 mutation carriers in Denmark | Enhanced Reader. PLoS One. 2018; 13(e0190050): 1-11.
3. Hu H, Liu J, Liao X, Zhang S, Li H. Genetic and functional analysis of a Li Fraumeni syndrome family in China. Sci Rep. 2016; 6.
4. Li FP, Fraumeni JFJ. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 1969; 71(4): 747-52.
5. Li FP, Fraumeni JFJ, Mulvihill JJ, Blattner WA, Dreyfus MG. A cancer family syndrome in twenty-four kindreds. Cancer Res. 1988; 48(18): 5358-62.
6. Gargallo P, Yáñez Y, Segura V, Juan A, Torres B, Balaguer J. Li–Fraumeni syndrome heterogeneity. Vol. 22, Clinical and Translational Oncology. Springer. 2020; 978-88.
7. Giacomazzi CR, Giacomazzi J, Netto CBO, Santos-Silva P, Selistre SG. Pediatric cancer and Li-Fraumeni/Li-Fraumeni-like syndromes: A review for the pediatrician. Vol. 61, Revista da Associacao Medica Brasileira. Associacao Medica Brasileira. 2015; 282-9.
8. Hendrickson PG, Luo Y, Kohlmann W, Schiffman J, Maese L. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: A hereditary cancer registry study. Cancer Med. 2020; 9(21): 7954-63.
9. Petry V, Bonadio RC, Cagnacci AQC, Senna LAL, Campos R do NG. Radiotherapy-induced malignancies in breast cancer patients with TP53 pathogenic germline variants (Li–Fraumeni syndrome). Fam Cancer. 2020; 19(1): 47-53.
10. Aubrey BJ, Strasser A, Kelly GL. Tumor-suppressor functions of the TP53 pathway. Cold Spring Harb Perspect Med. 2016; 6(5).
11. Mijit M, Caracciolo V, Melillo A, Amicarelli F, Giordano A. Role of p53 in the regulation of cellular senescence. Biomolecules. 2020; 10(3): 1-16.
12. Patil MR, Bihari A. A comprehensive study of p53 protein. J Cell Biochem. 2022; 123(12): 1891-937.
13. Krause A, Seymour H, Ramsay M. Common and Founder Mutations for Monogenic Traits in Sub-Saharan African Populations. Annu Rev Genom Hum Genet. 2025; 19:10.
14. Olivier M, PA, de CFC, & HP. TP53 Mutations in Human Cancers: Selection versus Mutagenesis [Internet]. Ayeda Ayed TH, editor. Vol. 4. Boston, MA: Springer US. 2010; 1-18 p.
15. Malkin D. Li-fraumeni syndrome. Genes Cancer. 2011; 2(4): 475-84.
16. Rocca V, Blandino G, D'Antona L, Iuliano R, Di Agostino S. Li–Fraumeni Syndrome: Mutation of TP53 Is a Biomarker of Hereditary Predisposition to Tumor: New Insights and Advances in the Treatment. Cancers (Basel). 2022; 14(15).
17. Amadou A, Waddington Achatz MI, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018; (30(1): 23-9.
18. Guha T, Malkin D. Inherited TP53 Mutations and the Li-Fraumeni syndrome. Cold Spring Harbor Perspect Med. 2017; a026187(7(4)): 1-12.
19. Chan CS. Prevalence and penetrance of Li-Fraumeni cancer predisposition syndrome. Vol. 1, Current Opinion in Systems Biology. Elsevier Ltd. 2017; 48-53.
20. Shin SJ, Dodd-Eaton EB, Peng G, Bojadzieva J, Chen J, Amos CI. Penetrance of different cancer types in families with Li-Fraumeni syndrome: A validation study using multicenter cohorts. Cancer Res. 2020; 80(2): 354-60.
21. Daly MB, Pal T, Maxwell KN. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024 Featured Updates to the NCCN Guidelines. JNCCN Journal of the National Comprehensive Cancer Network. 2023; 21(10): 1001-1010.
22. NCCN (Comprehensive Cancer Network N. NCCN Guidelines for Patients: Genetic Testing for Hereditary Breast, Ovarian, Pancreatic, and Prostate Cancers. Version 3.2024.
23. Schneider K, Zelley K, Nichols KE, Levine S, Garber J. Li-Fraumeni Syndrome. GeneReviews®[Internet]. 2025; 1-26.
24. Kratz CP, Achatz MI, Brugieres L, Frebourg T, Garber JE. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clinical Cancer Research. 2017; 23(11): e38-45.

25. Chompret A. Sensitivity and predictive value of criteria for p53germline mutation screening. J Med Genet. 2001; (38): 43-7.
26. A Chompret, A Abel, D Stoppa-Lyonnet. Criteria for P53 Germline Mutation. J Med Genet. 2001; 38: 43-7.
27. Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY. Beyond li fraumeni syndrome: Clinical characteristics of families with p53 germline mutations. Journal of Clinical Oncology. 2009; 27(8): 1250-6.
28. Wu CC, Shete S, Amos CI, Strong LC. Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res. 2006; 66(16): 8287-92.
29. Kuba MG, Lester SC, Bowman T, Stokes SM, Taneja KL. Histopathologic features of breast cancer in Li–Fraumeni syndrome. Modern Pathology. 2021; 34(3): 542-8.
30. Masciari S, Dillon DA, Rath M, Robson M, Weitzel JN. Breast cancer phenotype in women with TP53 germline mutations: A Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012; 133(3): 1125-30.
31. Verdial FC, Etzioni R, Duggan C, Anderson BO. Demographic changes in breast cancer incidence, stage at diagnosis and age associated with population-based mammographic screening. J Surg Oncol. 2017; 115(5): 517-22.
32. Sandoval RL, Polidorio N, Leite ACR, Cartaxo M, Pisani JP. Breast Cancer Phenotype Associated with Li-Fraumeni Syndrome: A Brazilian Cohort Enriched by TP53 p.R337H Carriers. Front Oncol. 2022; 12(March): 1-7.
33. Khincha PP, Best AF, Fraumeni JF, Loud JT, Savage SA, Achatz MI. Reproductive factors associated with breast cancer risk in Li–Fraumeni syndrome. Eur J Cancer. 2019; 116: 199-206.
34. Olsson H, Magnusson S, Bladström A. Lower breast cancer survival in mothers of children with a malignancy: A national study. Br J Cancer. 2008; 98(11):1876-8.
35. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, Obeid E, Liu DD. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. 2013; 118(4): 908-13.
36. Young Anampa J, Nandikolla A, Venugopal S. Breast cancer in patients with Li-Fraumeni syndrome a case series study and review of literature. Breast Cancer: Targets and Therapy. 2017; 9: 207-15.
37. Sasakı R, Horımoto Y, Saekı H, Sato S, Sano K. Lessons Learned in Practice with Li-Fraumeni Syndrome: LFS-Related Breast Cancer Treatment Strategy and Establishment of a Surveillance System. Juntendo Medical Journal. 2022; 68(4): 405-12.
38. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016; 122(23): 3673-81.
39. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: Sex differences in cancer risk. Am J Hum Genet. 2003; 72(4): 975-83.
40. Siegel A, Bremer RC, Klein WMP, Savage SA, Loud JT, Khincha PP. Uptake and timing of bilateral and contralateral risk-reducing mastectomy in women with Li–Fraumeni syndrome. Breast Cancer Res Treat. 2022; 191(1): 159-67.
41. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol [Internet]. 2016; 17(9): 1295-305.
42. National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast O and P. 2024.
43. National Cancer Institute (NCI). Adolescents and young adults (AYAs) with cancer. 2024.
44. Sánchez-Heras AB, Ramon y Cajal T, Pineda M, Aguirre E, Graña B, Chirivella I, et al. SEOM clinical guideline on heritable TP53-related cancer syndrome (2022). Clinical and Translational Oncology. 2023; 25(9): 2627-33.
45. Kumamoto T, Yamazaki F, Nakano Y. Medical guidelines for Li–Fraumeni syndrome 2019, version 1.1. Int J Clin Oncol. 2021; 26(12): 2161-2178.
46. Comeaux JG, Culver JO, Lee JE. Risk-reducing mastectomy decisions among women with mutations in high- and moderate- penetrance breast cancer susceptibility genes. Mol Genet Genomic Med. 2022; 10(10): 1-11.
47. Teoh V, Tasoulis MK, Gui G. Contralateral prophylactic mastectomy in women with unilateral breast cancer who are genetic carriers, have a strong family history or are just young at presentation. Vol. 12, Cancers. MDPI AG; 2020.
48. CDC- Breast Cancer in Young Women Bring Your Brave. 2024.
49. Ager B, Butow P, Jansen J, Phillips KA. Contralateral prophylactic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. Breast. 2016; 28: 107-20.
50. Chiesa Federica; Chiesa, Federica VSacchini. HHS Public Access. Physiol Behav. 2017; 176(10): 139-48.
51. Napoli M, Lewis J, Hopper J, Widmeyer K. Factors that impact risk management decisions among women with pathogenic variants in moderate penetrance genes associated with hereditary breast cancer. J Genet Couns. 2020; 29(6): 960-70.
52. Kaidar-person O, Offersen B V, Boersma LJ, Poortmans P. A multidisciplinary view of mastectomy and breast reconstruction: Understanding the challenges. 2021; 56.
53. Ferrari A, Stark D, Peccatori FA, Fern L, Laurence V. Adolescents and young adults (AYA) with cancer: a position paper from the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE). ESMO Open [Internet]. 2021; 6(2): 100096.
54. Janssen SHM, van der Graaf WTA, van der Meer DJ, Manten-Horst E, Husson O. Adolescent and young adult (Aya) cancer survivorship practices: An overview. Cancers (Basel). 2021; 13(19): 1-23.
55. Forbes Shepherd R, Lewis A, Keogh LA, Werner-Lin A. A systematic review of how young people live with inherited disease: What can we learn for li-fraumeni syndrome? J Adolesc Young Adult Oncol. 2018; 7(5): 525-45.
56. Forbes Shepherd R, Keogh LA, Werner-Lin A. Benefits and burdens of risk management for young people with inherited cancer: A focus on Li-Fraumeni syndrome. Aust J Gen Pract. 2021; 50(8): 538-44.

57. Hasson SP, Menes T, Sonnenblick A. Comparison of patient susceptibility genes across breast cancer: Implications for prognosis and therapeutic outcomes. Pharmgenomics Pers Med. 2020; 13: 227-38.

58. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA- Journal of the American Medical Association. 2017; 317(23): 2402–16.

59. Rising CJ, Wilsnack C, Boyd P, Sleight AG, Hutson P. Patient Education and Counseling Family communication challenges of adolescents and young adults with Li-Fraumeni syndrome: Implications for psychosocial care. 2022; 105(March): 3259-66.

60. Budych K, Helms TM, Schultz C. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. Health Policy (New York). 2012; 105(2-3): 154-164.