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Upper Gastrointestinal Cancer Risk and Surveillance Outcomes in Li-Fraumeni Syndrome

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Abstract

INTRODUCTION: To assess the upper gastrointestinal (UGI) cancer risk and surveillance outcomes in Li-Fraumeni syndrome (LFS).

METHODS: Analysis of the International Agency for Research on Cancer database and a single-center adult LFS cohort.

RESULTS: UGI cancer was present in 7.2% of families and 3.9% of individuals with a pathogenic/likely pathogenic *TP53* mutation in International Agency for Research on Cancer; 29% occurred before age 30. Our institutional cohort had 35 individuals (31% of the LFS cohort) with 48 cumulative upper endoscopies; 3 (8.5%) individuals had concerning UGI findings.

DISCUSSION: UGI cancer is observed in LFS. Upper endoscopy should be part of a comprehensive LFS surveillance program.

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CONFLICTS OF INTEREST

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INTRODUCTION

Li-Fraumeni syndrome (LFS) is an autosomal dominant syndrome caused by pathogenic/likely pathogenic (P/LP) germline variants in the *TP53* gene (1). LFS confers an 80%–90% lifetime risk of cancer with up to 21% of cancers occurring before age 15 (1). Increased gastrointestinal cancer risk has been reported, with several studies demonstrating increased colorectal cancer (CRC) risk in LFS, including at young ages (2,3). CRC surveillance guidelines for LFS carriers currently recommend colonoscopy starting at age 25, or 5 years before the earliest CRC in the family, with a 2- to 5-year interval (4,5).

Despite reported gastric and esophageal cancer risk in LFS (6), there are limited data characterizing the upper gastrointestinal (UGI) cancer risk. A 2011 report examining 62 families with LFS demonstrated 22.6% of families had documented or reported history of gastric cancer, with a median age at diagnosis of 36 years (7). This alludes to increased risk and younger age of gastric cancer onset in LFS; however, data on other UGI cancers are limited. Although upper endoscopy was not previously routinely recommended for LFS surveillance (8,9), the potential need for UGI cancer surveillance was recognized in 2015 (10), with subsequent recommendations to initiate upper endoscopy in LFS beginning at age 25 and repeating every 2–5 years, similar to colonoscopy recommendations (4,5). However, the yield and uptake of UGI surveillance in LFS remain unstudied.

In this article, we report the UGI cancer rates in individuals with germline P/LP variants in *TP53* included from the International Agency for Research on Cancer (IARC) database, as well as uptake and outcomes of UGI surveillance in a single institution cohort of individuals with LFS.

METHODS

Data from individuals with a known germline *TP53* variant were downloaded from the IARC database, version R20, download date: February 1, 2020 (11). All *TP53* variants were annotated with ANNOVAR (12), classified according to American College of Medical Genetics guidelines (13), and modified by ClinGen specific rules for *TP53* (14). Only individuals with *TP53* variants classified as P/LP were analyzed; dual mutation carriers were excluded. Cases of esophageal, gastric, and small intestinal cancers, including age of onset, were obtained. Under a University of Pennsylvania Institutional Review Board–approved protocol, clinical data were abstracted and reviewed for individuals (age 18 years or older) with a germline P/LP *TP53* variant seen at the University of Pennsylvania.

RESULTS

The R20 IARC database contained 3,043 individuals from 1,243 families with a germline P/LP *TP53* variant (Table 1). In this cohort, 3.9% of individuals and 7.2% of families had a history of an UGI cancer. Of the 90 families with an UGI cancer, 81 had at least 2 generations reported; 23% of those families had more than 1 UGI cancer reported. Gastric cancer, present in 3.3% of individuals, was the most common UGI cancer. Of note, 1.1% of individuals within this LFS cohort had an UGI cancer before age 30, representing 29% of all UGI cancers.

Our single-center cohort of 111 individuals with germline P/LP *TP53* variants, from 84 families, had 73% women and 91% who were living at the time of data collection, with a median age of 38 years (range 18–76 years, Table 2). Of this group, 75.7% had at least 1 previous malignancy, although none were UGI malignancies. Family history of UGI malignancy was documented for 7.2% of the individuals and 8.3% of the families in the cohort, with esophageal cancer being most commonly reported and no cancers reported before age 30.

Sixty-nine individuals attended genetics appointments at our institution since 2018 after upper endoscopy was added to LFS surveillance guidelines. Forty-five (65.2%) individuals had not yet undergone an upper endoscopy at the time of the appointment to satisfy surveillance recommendations. Upper endoscopy was recommended for 37 (82.2%) of these 45 individuals at their appointment. Age younger than 25 years was the most common reason upper endoscopy was not recommended (n = 4, 8.9%).

Overall, 35 individuals had 48 total upper endoscopies, and 40 reports were available for review. The most common findings included fundic gland polyps (n = 11) and gastritis (n = 6). No UGI cancers were identified; however, concerning UGI pathologic findings observed in 3 individuals included incidental eosinophilic esophagitis, a fundic gland polyp with low-grade dysplasia, and a duodenal adenoma.

DISCUSSION

LFS is a high-risk cancer syndrome; therefore, cancer surveillance in at-risk individuals is of the utmost importance. Although UGI surveillance is recommended in LFS, limited data support this recommendation. Here, we present the frequency of UGI cancers and the yield of upper endoscopy surveillance in individuals with LFS due to a P/LP *TP53* variant.

IARC database analysis identified UGI cancers among 3.9% of LFS individuals, which is similar to previous reports of UGI cancer in LFS (1,15). Of concern, 29% of the IARC UGI cancers occurred before age 30. Of the LFS families in IARC, 7.2% had an UGI cancer, similar to our institutional cohort; however, the IARC cohort had more gastric cancer compared with more esophageal cancer in our cohort possibly because of differing geographic representations of the cohorts. However, these numbers are substantially lower than the 22.6% of families previously reported with UGI cancer (7) and may indicate that a reported family history of UGI cancer may at times be inaccurate. Although some IARC families with more than 1 reported generation had multiple cases of UGI cancer, 77% of patients with an UGI cancer did not have a family history of UGI cancer reported, suggesting we cannot apply surveillance only in family history positive cases. The recommended UGI surveillance modality in LFS is upper endoscopy (4,5), similar to other UGI cancer risk syndromes (16), and our analysis of the IARC data supports current recommendations for upper endoscopy surveillance in LFS.

Our institutional data show that most patients with LFS had upper endoscopy recommended after LFS surveillance guidelines were changed. A subset of upper endoscopies revealed concerning and premalignant findings, which may be considered “surveillance successes.”

Further longitudinal data from upper endoscopies for LFS surveillance are necessary to determine benefit and optimal age of initiation and surveillance interval. In addition, although not explicitly stated in guidelines, providers performing upper endoscopy for LFS surveillance should consider routine assessment for *Helicobacter pylori*, with treatment if positive, to decrease gastric cancer risk. Similar recommendations are made for Lynch syndrome (16). Limitations of our work include potentially inaccurate reports of cancer history in IARC and the relatively small number of upper endoscopies in our LFS cohort.

In conclusion, LFS is a highly penetrant cancer predisposition syndrome with an increased risk of early-onset UGI cancers, although upper gastrointestinal cancer risk in LFS may be lower than previously reported. Upper endoscopy should be offered as part of a comprehensive LFS surveillance protocol.

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Table 1.

UGI tract cancer in individuals with Li-Fraumeni syndrome in the International Agency for Research on Cancer database

	n	%
Individuals		
Individuals with an LP/P variant	3,043	—
Individuals with esophageal cancer	15	0.5
Individuals with gastric cancer	101	3.3
Individuals with small intestinal cancer	2	0.1
Individuals with any UGI cancer	118	3.9
Individuals with any UGI cancer under 30	34	1.1
Families		
Families with an LP/P variant	1,243	—
Families with esophageal cancer	15	1.2
Families with gastric cancer	73	5.9
Families with small intestinal cancer	2	0.2
Families with any UGI cancer	90	7.2
Families with any UGI cancer under 30	28	2.3

LP/P, likely pathogenic/pathogenic; UGI, upper gastrointestinal.

Table 2.

LFS cohort demographic and clinical characteristics

	n	%
Individuals		
Individuals in the LFS cohort	111	—
Female sex	81	73.0
Living	101	91.0
Previous cancer diagnosis	84	75.7
1 previous cancer diagnosis	38	34.2
2 previous cancer diagnoses	24	21.6
3 or more previous cancer diagnoses	22	19.8
Family history of any UGI cancer	8	7.2
Family history of any UGI cancer under 30	0	—
Family history of esophageal cancer	5	4.5
Family history of gastric cancer	3	2.7
Family history of small intestinal cancer	0	—
Families		
Families in the LFS cohort	84	—
Family history of any UGI cancer	7	8.3
Family history of any UGI cancer under 30	0	—
Family history of esophageal cancer	5	6.0
Family history of gastric cancer	3	3.6
Family history of small intestinal cancer	0	—

LFS, Li-Fraumeni syndrome; UGI, upper gastrointestinal.