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Earlier colorectal cancer screening may be necessary in patients with Li-Fraumeni Syndrome

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Introduction

Li-Fraumeni Syndrome (LFS) is an autosomal dominant inherited cancer predisposition syndrome caused by germline mutations in *TP53*. LFS is characterized by an 80–90% lifetime risk of a broad spectrum of cancers, of which 21% of cancers occur by age 15.[1–3] Established cancer screening guidelines for LFS patients lead to earlier cancer detection and treatment.[3] Colorectal cancer (CRC) screening recommendations in LFS advise initiating screening at age 25, or 10 years prior to the first familial case of CRC.[4] Incidence of early-onset CRC in previously published reports suggest that the frequency of CRC was at least 0.7% under age 25, and at least 2.8% under age 50, with a median age of onset 33–38 years; [1, 5] in one study including polyps with high-grade dysplasia (HGD), this frequency increased to 6.1% under 25 and 7.6% under 50 years.[6]

We performed a retrospective review to determine CRC incidence in a clinically wellannotated cohort of LFS patients at a pediatric/adult medical center. We also conducted a focused review of CRC in individuals with pathogenic *TP53* mutations included in the International Agency for Research on Cancer (IARC). In light of available literature and collected data, further studies are needed to determine if colonoscopy or alternative non-invasive colon cancer screening modalities are beneficial at a younger age, especially in patients who received abdominal radiation.

Methods

Children's Hospital of Philadelphia (CHOP)/University of Pennsylvania (Penn) data review:

Under CHOP and Penn Institutional Review Board approved protocols, medical records were queried over a 10-year period (2007–2017) to identify individuals with a confirmed pathogenic germline mutation in *TP53*; cases were cross-referenced with cancer predisposition records.

Medical records and pathology were then reviewed for a diagnosis of colon adenocarcinoma, colorectal adenocarcinoma, rectal adenocarcinoma, or HGD in a colonic adenoma.

IARC Data Review:

Data were downloaded from the IARC database[7] for individuals with known germline *TP53* mutations. *TP53* mutations were classified as pathogenic/likely pathogenic in 1990 individuals in 727 families, and all other genetic alterations were excluded. The incidence of colon cancer, colorectal cancer, or rectal cancer was determined for all individuals.

Results

Review of records at CHOP and Penn are detailed in **Table 1.** In the combined cohort of 93 *TP53*+ LFS patients, 67.7% had a diagnosis of at least one malignancy. Of 93 patients, 8.6% had a diagnosis of either CRC or adenomatous polyp with HGD (Table 1); 3.2% had a CRC

diagnosis before age 25 (age range 15–20 years) and 4.3% before age 35. Of those diagnosed with CRC, three had a history of a prior malignancy, and one pediatric patient had a history of abdominal radiation. None of patients had family history of CRC under the age of 35 years.

Of 1990 individuals with clinically pathogenic mutations in *TP53* in the IARC dataset, 70 (3.5%) had a diagnosis of CRC, with age stratification detailed in Table 1. Fifty-six of 727 families (7.7%) had at least one family member diagnosed with CRC. Overall in IARC, 16% of the 70 CRC diagnoses occurred in individuals under age 25, and 17% between ages 25 and 34.

Discussion

Leveraging the in-depth medical records of a large pediatric/adult tertiary care referral center, we found the incidence of early onset CRC/HGD in LFS patients to be 8.6%, with three patients (3.2%) diagnosed prior to age 25. Our review of the IARC database demonstrated a 3.5% incidence of CRC in individuals with clinically pathogenic *TP53* mutations, with 1% diagnosed with CRC under age 25. Although these data are supported by previous reports of CRC incidence in LFS, this is the largest single-institution combined pediatric/adult cohort of CRC/HGD incidence in LFS to date.[1] Additionally, though patients were not selected other than by period of study, this study may be subject to ascertainment bias, given variable penetrance in LFS.

Adult screening protocols recommend colonoscopy at the age when CRC risk is 0.6% or greater, [8] given the improved outcomes with early detection. When data from this cohort, the IARC database, and previous studies are viewed together, the incidence of CRC in LFS is at least 0.6% under age 25. We suggest that initiation of screening colonoscopy or other noninvasive colon cancer screening modalities should be considered earlier in the LFS population, especially in pediatric patients who received abdominal radiation. In conclusion, a subset of LFS patients are at increased risk to develop CRC at a young age, and thus earlier CRC screening should be considered in this population to help mitigate the increased CRC risk.

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Abbreviations:

LFS	Li-Fraumeni Syndrome
CRC	Colorectal Cancer
HGD	High Grade Dysplasia
IARC	International Agency for Research in Cancer

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Table 1

: CRC Diagnosis by age in patients with LFS

	IARC			CHOP/PENN		
n[1]	1990			93		
	CRC			CRC	CRC or HGD	
	n	%	n	%	n	%
Total	70	3.5%	5	5.4%	8	8.6%
<=25 years	11	0.6%	3	3.2%	3	3.2%
<=35 years	28	1.4%	4	4.3%	4	4.3%
<=50 years	49	2.5%	5	5.4%	8	8.6%

[1]Total number of individuals with a likely pathogenic/pathogenic mutation in *TP53*