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Accessibility
Gastric Cancer in Individuals with Li-Fraumeni Syndrome

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Abstract

PURPOSE—Li-Fraumeni Syndrome (LFS) is a rare hereditary cancer syndrome associated with germline mutations in the TP53 gene. While sarcomas, brain tumors, leukemias, breast and adrenal cortical carcinomas are typically recognized as LFS- associated tumors, the occurrence of gastrointestinal neoplasms has not been fully evaluated. In this analysis, we investigated the frequency and characteristics of gastric cancer (GC) in LFS.

METHODS—Pedigrees and medical records of 62 TP53 mutation-positive families were retrospectively reviewed from the Dana-Farber/National Cancer Institute LFS registry. We identified subjects with GC documented either by pathology report or death certificate, and performed pathology review of the available specimens.

RESULTS—Among 62 TP53 mutation-positive families, there were 429 cancer-affected individuals. GC was the diagnosis in the lineages of 21 (4.9%) subjects from 14 families (22.6%). The mean and median ages at GC diagnosis were 43 and 36 years, respectively (range 24-74 years), significantly younger compared to the median age at diagnosis in the general population based on SEER data (71 years). Five (8.1%) families reported 2 or more cases of GC and 6 (9.7%) families had cases of both colorectal and gastric cancers. No association was seen between

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phenotype and type/location of the TP53 mutations. Pathology review of the available tumors revealed both intestinal and diffuse histologies.

CONCLUSIONS—Early-onset GC appears to be a component of LFS, suggesting the need for early and regular endoscopic screening in individuals with germline TP53 mutations, particularly among those with a family history of GC.

Keywords
Li Fraumeni syndrome; gastric cancer; hereditary gastric cancer syndromes; germline mutations; TP53

INTRODUCTION
Gastric cancer is one of the most common cancers worldwide and a leading cause of cancer-related mortality. In 2010, it is estimated that 21,000 new cases of gastric cancer were diagnosed in the United States alone and approximately 50% of affected individuals died from the disease. Although the majority of gastric cancers are sporadic, about 10% are familial. Among the latter group, germline mutations in the CDH1 gene account for 30-40% of the rare syndrome known as Hereditary Diffuse Gastric Cancers (HDGC). Gastric cancers also occur, but less frequently, as a component of other hereditary cancer syndromes (Table 1).

Li-Fraumeni Syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the TP53 tumor suppressor gene. Sarcomas of soft tissue and bone, brain tumors, leukemias, breast and adrenal cortical carcinomas are classically included in the LFS tumor spectrum. Additional studies have shown that individuals with germline TP53 mutations have an increased risk of a broad range of neoplasms, including carcinomas of the lung, gonadal germ cell tumors, melanomas and lymphomas.

Our group has previously shown that the prevalence of early-onset (age <50 years) colorectal cancer is increased in LFS families. This finding led to the inclusion of surveillance colonoscopy as part of the management approach in TP53 mutation carriers in the National Comprehensive Cancer Network (NCCN) guidelines.

As the occurrence of gastric cancer in TP53 mutation carriers has not been well documented, we searched the LFS family registry of the Dana-Farber Cancer Institute and National Cancer Institute to assess the number of cases and ages at diagnosis of gastric cancer in individuals and families with classic LFS or LFS-like histories and germline TP53 mutations. In cases with gastric cancer, we examined whether there were any genotype-phenotype associations, and performed central pathological review of available tumor specimens.

MATERIALS AND METHODS

Subject Selection
Subjects were from families previously enrolled in the Dana-Farber Cancer Institute/National Cancer Institute (DFCI/NCI) LFS family registry. This registry was originally assembled by Drs. Li and Fraumeni in 1969; new families have been added via self or physician referral. The registry includes families who meet the classic LFS criteria, with or without identified TP53 gene mutations.
The registry is maintained under a clinical protocol reviewed and approved annually by the Dana Farber/Harvard Cancer Center Institutional Review Board.

The analysis was limited to families with identified pathogenic TP53 mutations. Each pedigree was reviewed to assign the lineage that was the likely source (maternal or paternal) of the TP53 mutation. Pedigrees and available medical record data were reviewed to provide the number, age at diagnosis and histologic features of gastric cancers in the affected lineage of these families, and to evaluate the occurrence of other gastrointestinal tumors. We then looked at the different types of TP53 mutations to explore potential genotype/phenotype correlations. The age range, mean and median ages of diagnosis for the gastrointestinal tumors were calculated. We used Wilcoxon Rank Sum test to compare the median age at diagnosis of gastric cancer in our cohort to the corresponding age of gastric cancer in the general population using data from the Surveillance Epidemiology and End Results (SEER) database from 2001-2005.

Pathology Review

Pathology information was retrieved from medical records and death certificates, and tumor specimens were collected for all available cases of gastric cancers from the registry. In addition, gastric cancer specimens from documented TP53 mutation positive LFS kindreds were provided by our Brazilian collaborators. These cases from Brazil were included only in the pathology review, but not in the frequency analysis of GC. Histological review was performed by a single gastrointestinal pathologist (GYL).

The location of the tumors, histologic type based on the Lauren classification, and stage were determined along with the presence of any precursor lesions, such as gastric dysplasia, intestinal metaplasia, and chronic active gastritis related to Helicobacter pylori infection.

RESULTS

Among 312 families reported in the LFS registry, 62 had confirmed pathogenic TP53 mutations. A total of 429 individuals in the affected lineage of the 62 families had been diagnosed with one or more cancers. Gastric or gastro-esophageal junction cancers (here considered as gastric cancer) were diagnosed in 21 (4.9%) individuals from 14 families (Table 2). Nine gastric cancers (42.9%) were confirmed either by medical and pathological records or by death certificates while the remaining 12 cases were reported by family history. Overall, the mean and the median ages at diagnosis of gastric cancer were 43 years and 36 years, respectively (range 24-74 years). The mean and median ages at diagnosis of the 9 confirmed cases of gastric cancer were 46 and 36 years, respectively (range 24-74 years), including 5 subjects with gastric cancer before age 40. Twelve of the 21 (57.1%) cases of gastric cancer in LFS families were diagnosed before age 45 years, with 4 subjects diagnosed before age 30 (the youngest, 24 years). Of note, the individual with documented gastric cancer at 74 years of age was a confirmed mutation carrier. The median age at diagnosis of gastric cancer in this group was significantly younger (p<0.0001) compared to the SEER dataset (Figure 1).

Thirty-two (51.6%) of the 62 families had at least one family member with gastrointestinal cancer, including gastric, esophageal, colorectal or pancreatic cancers. There were 14 (22.6%) families with one or more cases of gastric cancer, 5 families (8.1%) with two or more cases of gastric cancer, and 6 (9.6%) families with cases of both gastric and colorectal cancers. In examining the pedigrees of the 62 families for additional gastrointestinal tumors occurring in the affected lineage, we found 28 (4.8%) colorectal cancers (median age at diagnosis of 53.0 years) and 7 (1.2%) pancreatic cancers (median age of 60.5 years).
Overall, 17 (27.4%) of 62 families had cases of gastric or colorectal cancer diagnosed before age 50 years.

Details of TP53 mutation type were available for all families with gastric cancer cases. Two families (families 4 and 11 shown in figure 2) had the same mutation in exon 6 (Arg213X). However, the other 12 families had 12 different mutations distributed along exons 4 to 10 with no clear genotype-phenotype correlation (Table 2).

**Characteristics of gastric tumors**

Histologic material was available for 5 of the 9 confirmed cases of gastric cancer in the DFCI/NCI registry and the two additional cases obtained from Brazil (Table 4). Four of the 7 tumors arose in the proximal region of the stomach, two in the antrum, and one in the fundus; all were advanced at the time of diagnosis. Five of the cases had an intestinal morphotype (3 moderately differentiated and 2 well differentiated) while two had the diffuse type with signet ring cells (Figure 3). Two of the tumors were diagnosed at stage pT2, four at stage pT3 and one at stage pT4. Of note, one of the cases from Brazil was a 12 year old who had metastatic gastric cancer at presentation.

Gastric dysplasia was not identified in any of the histopathologic material available for review. Very focal intestinal metaplasia was noted in a single case, while two cases had features suggestive of Helicobacter pylori inflammation. Although stains for this organism had not been performed, one case had prominent lymphoid hyperplasia and another had chronic active gastritis in the surrounding mucosa.

**DISCUSSION**

In our series of 62 families with TP53 mutations in the DFCI/NCI LFS family registry, 14 (22.6%) families had at least one member diagnosed with gastric cancer. Of 429 family members with cancer, 21 had gastric cancer (4.9%). Similar to other hereditary cancer syndromes, the age at diagnosis of gastric cancer in LFS was much younger than in the general population in the United States (median age at diagnosis at 36 years versus 71 years, p<0.0001). Although the tumors specimens available for review were limited in number and amount of tissue, both intestinal and diffuse type gastric cancers were seen, with 50% of the tumors located in the proximal stomach.

Although literature surveys indicate that gastric cancer is an uncommon manifestation of LFS, its occurrence has featured a remarkably young age at diagnosis. In 2001, Nichols et al reported that among 738 cancer-affected TP53 mutation carriers and their first-degree relatives from the original DFCI/NIH LFS registry and from the review of the literature through 1999, there were 23 (3.1%) cases of carcinoma of the stomach17. The International Agency for Research on Cancer (IARC) TP53 Mutation Database30 compiles all kindreds with TP53 mutations reported in the published literature since 1989 (DFCI/NCI families are not included). Among 899 tumors reported in individuals with TP53 germline mutations, only 16 (1.8%) are gastric tumors. Based on case reports of LFS or LFS-like families associated with TP53 mutations in Japan and Korea, gastric cancer in LFS seems more prevalent in Asian populations with high rates of gastric cancer31-35. This finding suggests that individuals with germline TP53 mutation are susceptible to the carcinogenesis effects of Helicobacter pylori infection in endemic areas. The interaction may be analogous to the smoking-related lung cancer and the radiation-related sarcomas reported in LFS. These studies also suggest that TP53 mutations may be informative in families with early onset gastric cancer, especially when more characteristic LFS-related tumors are present in the families. Of note, sporadic TP53 mutations can be found in almost every tumor with a prevalence of sporadic mutations in stomach cancer of 20%36.
While adding to previous data on the occurrence of gastric cancer in LFS families, our study has limitations based on its retrospective nature, incomplete and missing data, and inability to confirm the cancer diagnoses and genotypes for all subjects. Although gastric cancers on average were diagnosed at much younger ages than the SEER population, some of the tumors occurred at ages above 50 years. As not all individuals with gastric cancer had mutation testing, some of the cancers at older ages may have represented sporadic cases. Furthermore, there is always a risk of misclassification associated with abdominal tumors, since the site of origin may be difficult to discern, even at surgery. These factors may have contributed to an overestimate of TP53 mutations associated with gastrointestinal tumors.

To minimize these errors, we carefully reviewed each pedigree and excluded gastric cancers that were either on the unaffected side of the family or were distant from the proband with the pathogenic TP53 mutation. We also attempted to confirm as many gastric cancer diagnoses as possible. Previous studies evaluating the completeness and accuracy of family history reporting of cancers have found satisfactory reporting of gastrointestinal and intra-abdominal tumors by family members. In addition, the majority (81%) of gastric cancer cases in our study were either probands or first- and second-degree relatives of mutation carriers. Prior studies have reported that the degree of closeness to an affected relative correlates with the accuracy of cancer reporting, which is highest for tumors among first-degree relatives.

Despite the difficulties of studying an uncommon manifestation of a rare syndrome, our findings suggest an excess occurrence of early-onset gastric cancer in TP53 mutation-positive families. The results are similar to our other observations on colorectal cancer in LFS, and may have implications for diagnostic and preventive interventions in selected families. Due to the broad array of cancers associated with LFS and the lack of effective screening modalities for most LFS-related cancers, such as sarcomas and brain tumors, the measures aimed at early cancer detection are limited. The only available guidelines for cancer screening in TP53 carriers are from the NCCN and suggest that screening for breast and colorectal cancers is advisable. Our group has reported a pilot study evaluating the role of whole-body PET (positron emission tomography)/CT (computerized tomography) scan in 15 LFS families. In that study a tumor of the gastro-esophageal junction was detected by scan and confirmed with esophago-gastro-duodenoscopy (EGD). Given the colonoscopy recommendations for surveillance of colorectal cancer, the addition of periodic screening with EGD in germline TP53 carriers may be reasonable to consider, particularly in LFS families in which at least one member has gastric cancer. The early age at diagnosis in comparison to the general population suggests that surveillance may need to begin in young adults. Nevertheless, we need to consider the data showing that upper GI endoscopies were frequently normal in patients with diffuse gastric cancer which was eventually diagnosed after prophylactic surgery. More data are needed to establish the effectiveness and appropriate intervals for screening with EGD in TP53 carriers, in addition to targeted interventions based on individual family history.

In summary, although it is an uncommon manifestation of LFS, early-onset gastric cancer appears to be a component of the spectrum of tumors that are associated with this familial syndrome. Further studies are needed to determine the role of EGD as well as other cancer detection measures among individuals with TP53 germline mutations.

Acknowledgments

We are grateful to the Li Fraumeni patients and families who kindly consented over the years to be part of the DFCI/NCI LFS registry.

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Abbreviations used in this paper

LFS Li-Fraumeni Syndrome
HDGC Hereditary Diffuse Gastric Cancer
DFCI/NCI Dana-Farber Cancer Institute/National Cancer Institute
LFL Li-Fraumeni-like
SEER Surveillance Epidemiology and End Results
IARC International Agency for Research on Cancer
NCCN National Comprehensive Cancer Network
PET/CT positron emission tomography/computerized tomography
EGD esophago-gastro-duodenoscopy

References


Figure 1.
Distribution of Gastric Cancer by Age in DFCI/NCI LFS registry and the SEER database
Figure 2.
Pedigree plots of 3 families (Families 4, 8 and 11) with multiple cases of early onset gastric cancers and a known TP53 mutation. The circles represent females while the squares represent males. Open symbols indicate no neoplasm and filled symbols represent those with cancer; crossed symbols indicate deceased individuals. Arrows indicate probands, all positive for a TP53 mutation. STO/GEJ, stomach/gastroesophageal junction cancer; BR, breast cancer; SS, soft-tissue sarcomas; OS, osteosarcoma; CNS, central nervous system cancer; CO, colon cancer; PAN, pancreatic cancer; LG, lung cancer; ENDO, endometrial cancer; KID, kidney tumor; PR, prostate cancer; ACC, adrenal cortical cancer; TC, thyroid cancer. Numbers after the symbols for the type of cancer indicate age at death or age at diagnosis. The pedigrees have been de-identified to protect confidentiality. The pedigree of family 8 has been previously published.12
Figure 3.
Example of intestinal type moderately differentiated (A) and diffuse type gastric adenocarcinoma (B) observed in our cohort.
### Table 1

Gastric cancer in hereditary cancer syndromes.

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Gene Involved</th>
<th>Gastric Cancer Risk</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Diffuse Gastric Cancer</td>
<td>CDH1</td>
<td>67%-83%</td>
<td>Pharoa et al(^{39})</td>
</tr>
<tr>
<td>Syndrome (HDGC)</td>
<td></td>
<td></td>
<td>Kaurah et al(^{8})</td>
</tr>
<tr>
<td>Hereditary Non Polyposis Colorectal Cancer (HNPCC)</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>2%-30%</td>
<td>Koornstra et al(^{40})</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome (PJS)</td>
<td>STK11</td>
<td>29%</td>
<td>van Lier et al(^{41})</td>
</tr>
<tr>
<td>Hereditary Breast/Ovarian Cancer Syndrome (HBOC)</td>
<td>BRCA1</td>
<td>5.5%</td>
<td>Thompson et al(^{42})</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>2.6%</td>
<td>Breast Cancer Linkage Consortium(^{44})</td>
</tr>
<tr>
<td></td>
<td>APC</td>
<td>2.1%-4.2% *</td>
<td>Park et al(^{46})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Iwama et al(^{47})</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis (FAP)</td>
<td>SMAD4, BMPR1A</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome (JPS)</td>
<td>N/A</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Li-Fraumeni Syndrome (LFS) (^{a})</td>
<td>TP53</td>
<td>N/A</td>
<td>-</td>
</tr>
</tbody>
</table>

* This increased risk is for the Korean and Japanese populations. In other ethnicities the risk is the same as the general population.

\(^{a}\) The estimate of the gastric cancer risk has not been calculated for these conditions.
### Table 2

Spectrum of TP53 mutations and ages at diagnosis of gastric cancer in Li Fraumeni Syndrome Families with gastric cancer

<table>
<thead>
<tr>
<th>Family</th>
<th>Type</th>
<th>Mutation type in the family</th>
<th>Location of the mutation</th>
<th>Age at diagnosis of gastric cancers $^\wedge$</th>
<th>Additional primary in gastric cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LFL</td>
<td>Pro301delX344</td>
<td>Exon 8</td>
<td>27</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>2</td>
<td>LFS</td>
<td>Arg273His</td>
<td>Exon 8</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LFL</td>
<td>Cys275Phe</td>
<td>Exon 8</td>
<td>35</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>4</td>
<td>LFS</td>
<td>Arg213X</td>
<td>Exon 6</td>
<td>a.29</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.36</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>LFL</td>
<td>Pro152Leu</td>
<td>Exon 5</td>
<td>a.45</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.52</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>c.58</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>LFS</td>
<td>Glu339X</td>
<td>Exon 10</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>LFS</td>
<td>Arg273Cys</td>
<td>Exon 8</td>
<td>60</td>
<td>Soft Tissue Sarcoma</td>
</tr>
<tr>
<td>8</td>
<td>LFL</td>
<td>686-687delGT</td>
<td>Exon 7</td>
<td>a.74</td>
<td>NHL, Pancreatic Ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.31</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>LFS</td>
<td>Arg248Gln</td>
<td>Exon 7</td>
<td>59</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>LFS</td>
<td>Glu258Lys</td>
<td>Exon 7</td>
<td>a.24</td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.60</td>
<td>-</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>c.62</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>LFL</td>
<td>Arg213X</td>
<td>Exon 6</td>
<td>a.29</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b.32</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>LFL</td>
<td>Arg196X</td>
<td>Exon 6</td>
<td>31</td>
<td>-</td>
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<tr>
<td>13</td>
<td>LFS</td>
<td>Arg110Pro</td>
<td>Exon 4</td>
<td>32</td>
<td>-</td>
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<tr>
<td>14</td>
<td>LFS</td>
<td>Arg158His</td>
<td>Exon 5</td>
<td>32</td>
<td>-</td>
</tr>
</tbody>
</table>

NHL: Non-Hodgkin Lymphoma

$^\wedge$ Letters indicate different individuals with gastric cancers in the same family.
Table 3
Pathology Review of the available specimens

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Dx</th>
<th>Location</th>
<th>Histology</th>
<th>Grade</th>
<th>Stage</th>
<th>GED/IM</th>
<th>HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>F</td>
<td>29</td>
<td>Proximal stomach</td>
<td>DGC(SRC)</td>
<td>-</td>
<td>pT3</td>
<td>-/-</td>
<td>No evidence</td>
</tr>
<tr>
<td>4b</td>
<td>M</td>
<td>36</td>
<td>Proximal stomach</td>
<td>DGC(SRC)</td>
<td>-</td>
<td>pT3</td>
<td>-/-</td>
<td>No evidence</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>74</td>
<td>Antrum</td>
<td>IGC</td>
<td>3</td>
<td>pT2</td>
<td>-/-</td>
<td>Mild chronic inflammation</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>29</td>
<td>Proximal stomach</td>
<td>IGC</td>
<td>2</td>
<td>pT2</td>
<td>-/-</td>
<td>No evidence</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>35</td>
<td>Antrum</td>
<td>IGC</td>
<td>2</td>
<td>pT3</td>
<td>-/+</td>
<td>Mild chronic inflammation</td>
</tr>
<tr>
<td>B1</td>
<td>M</td>
<td>39</td>
<td>Fundus</td>
<td>IGC</td>
<td>3</td>
<td>pT3</td>
<td>-/-</td>
<td>No evidence</td>
</tr>
<tr>
<td>B2*</td>
<td>M</td>
<td>12</td>
<td>Proximal stomach</td>
<td>IGC</td>
<td>1</td>
<td>pT4</td>
<td>+/-</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

DGC: Diffuse gastric cancer; SRC: Signet Ring Cells; IGC: Intestinal type gastric cancer
GED: Gastric epithelial dysplasia; IM: Intestinal metaplasia; HP Helicobacter Pylori

*Mild chronic inflammation* inactive gastritis, is not a specific features of HP.

*The pathology report was available for review of the primary site. Liver and peritoneal metastasis images were available for review.