LI-FRAUMENI SYNDROME (LFS) is a rare hereditary cancer syndrome characterized by an increased predisposition to diverse early onset malignancies, including but not limited to sarcomas, breast cancers, brain tumors, adrenal cortical carcinomas, and leukemias.\(^1\) Germline mutations in the tumor suppressor gene TP53 (tumor protein p53, chromosome 17p13; OMIM 191170) are detectable in 70% of classic LFS families.\(^2,3\) Over time, the list of neoplasms occurring excessively in LFS has expanded to include a much broader range of cancers, including gastrointestinal tract and endocrine tumors and lymphomas.\(^4-7\) Individuals with LFS who survive one cancer have a markedly elevated risk of additional primary neoplasms.\(^8,9\)

In classic LFS, the proband must be diagnosed with a sarcoma before age 45 years, a first-degree relative with cancer before age 45 years, and another first-degree relative with soft tissue or osteosarcoma at any age, or any cancer before age 45 years.\(^1\) Li-Fraumeni–like kindreds have cancer histories meeting less stringent criteria, and a 30% chance of carrying a germline TP53 mutation.\(^10-12\) In individuals carrying TP3 mutations, the risk of developing cancer has

Context: Individuals with Li-Fraumeni syndrome (LFS) have an inherited cancer predisposition to a diverse array of malignancies beginning early in life; survivors of one cancer have a markedly elevated risk of additional primary cancers. The underlying genetic defect in the majority of the families is a germline mutation in the TP53 tumor suppressor gene. The diversity of tumors and rarity of families have contributed to the difficulty in devising effective screening recommendations for members of LFS kindreds.

Objective: To gather preliminary data with which to evaluate F18-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) imaging as a potential surveillance modality to detect early malignancies in asymptomatic members of LFS kindreds.

Design, Setting, and Participants: Members of LFS families with documented germline TP53 mutations or obligate carrier status, no history of cancer within 5 years of enrollment, and no symptoms of cancer or ill-health were offered FDG-PET/CT scanning as a screening test in a comprehensive US cancer center from 2006 to 2007. Scans were initially reviewed clinically, then centrally reviewed by an expert radiologist.

Main Outcome Measure: The primary outcome was the detection of new primary cancers using FDG-PET/CT scanning.

Results: Of 15 individuals, baseline FDG-PET/CT scan identified asymptomatic cancers in 3 (20%). Two individuals had papillary thyroid cancers (stage II and stage III) and one individual had stage II esophageal adenocarcinoma.

Conclusions: These preliminary data provide the first evidence for a potential cancer surveillance strategy that may be worthy of further investigation for patients with LFS. Concerns about radiation exposure and other challenges inherent in screening high-risk patients will require further consideration.

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been estimated at 50% by age 30 years and 90% by age 60 years. In LFS, tumors can occur in any anatomic site at any age, making it difficult to identify practical, effective screening and prevention strategies.

We explored the use of fluorodeoxyglucose F18–positron emission tomography/computed tomography (FDG-PET/CT) scanning for early detection in LFS kindreds because of its demonstrated ability to detect primary tumors as well as metastatic lesions in a wide range of neoplasms, including breast cancer, sarcomas, and aggressive brain tumors.

METHODS

Individuals were recruited from those responding to a survey mailed to members of 60 kindreds in the LFS family registry at the Dana-Farber Cancer Institute, which includes families originally enrolled at the National Cancer Institute. Participation also was offered to individuals contacting the Dana-Farber Cancer Institute for information about LFS. Eligible individuals were members of LFS kindreds who either carried a known TP53 mutation or were obligate mutation carriers. Participants were either cancer survivors or without a prior cancer history. Exclusion criteria included a prior history of metastatic cancer or a new invasive cancer diagnosis within the previous 5 years. All participants signed informed consent, provided a medical history, underwent a physical examination, and provided complete blood counts plus differential. The study was approved by the Dana-Farber/Harvard Cancer Center institutional review board. The study was conducted from 2006 to 2007.

FDG-PET/CT Imaging and Evaluation

The FDG-PET/CT scans were performed in accordance with the clinical protocols of the Dana-Farber Cancer Institute. The European Organization for Research and Treatment of Cancer and the National Cancer Institute’s guidelines on a hybrid system consisting of a combined PET/CT scanner (Biograph 16 Hi-Rez, Siemens, Knoxville, Tennessee; GE Discovery ST 16, Milwaukee, Wisconsin) were used.20,21 Individuals were instructed to avoid strenuous exercise and fast for at least 6 hours prior to being injected with approximately 20 mCi of FDG. A whole-body PET/CT scan was performed at 60 minutes postinjection of FDG. The spiral CT scan was performed with a moderate dose to enable anatomical localization in addition to correction of photon attenuation. The whole-body PET scan was performed immediately after the spiral CT scan for approximately 40 to 45 minutes (13-15 PET bed positions at 3 minutes per bed position). At the conclusion of the whole-body PET scan, a dedicated brain PET scan was performed for 15 minutes. The estimated effective dose of the entire FDG-PET/CT imaging session was approximately 2.4 rem.

A nuclear medicine physician experienced in reading FDG-PET/CT scans (A.V.D.A.) and aware of protocol eligibility criteria reviewed all images blinded to clinical history and prior clinical interpretation. Areas of increased focal FDG uptake were scored using a 5-point scale of likelihood that any finding was malignant (1, definitely benign; 2, probably benign; 3, equivocal; 4, probably malignant; 5, definitely malignant). The maximum standardized uptake values were measured for all lesions (data not shown). Data for the 3 individuals with a score of 4 or greater are reported in the Table. The protocol included a follow-up scan at 12 months (data not complete).

RESULTS

Of the 15 asymptomatic individuals with a physical examination not suspicious for cancer and normal complete blood cell count, FDG-PET/CT scanning detected lesions in 3 (20%). The lesions were identified as being likely malignant (score ≥4) and were subsequently confirmed as malignant (Table). A focus of moderately increased tracer uptake (maximum standardized uptake value of 5.2) in the right lobe of the thyroid in a 31-year-old breast cancer survivor was a stage II papillary thyroid carcinoma with thymus involvement (T1N0M1) at thyroidectomy. An intensely FDG-avid (maximum standardized uptake value of 17) nodule in the left lobe of the thyroid of a survivor of breast cancer and sarcoma was a stage III papillary carcinoma (T3N0M0) at resection (FIGURE 1). Finally, a 36-year-old asymptomatic male with no prior history of cancer showed an area of focal increased uptake (maximum standardized uptake value of 5.3) at the gastroesophageal junction (FIGURE 2).

Table. Features of Lesions Detected by Fluorodeoxyglucose F18–Positron Emission Tomography/Computed Tomography (FDG-PET/CT)

<table>
<thead>
<tr>
<th>No. of Individual</th>
<th>FDG-PET/CT Tracer Uptake</th>
<th>Maximum Standardized Uptake Value</th>
<th>Lesion Score</th>
<th>Additional Imaging</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>026</td>
<td>Thyroid, right lobe</td>
<td>5.2</td>
<td>4</td>
<td>Magnetic resonance imaging</td>
<td>Stage II thyroid carcinoma (T1N0M1)</td>
</tr>
<tr>
<td>014</td>
<td>Gastroesophageal junction</td>
<td>5.3</td>
<td>4</td>
<td>Esophagogastroduodenoscopy/ endoscopic ultrasound</td>
<td>Stage IIA esophageal adenocarcinoma (T3N0M0)</td>
</tr>
<tr>
<td>101</td>
<td>Thyroid, left lobe</td>
<td>17</td>
<td>5</td>
<td>Magnetic resonance imaging</td>
<td>Stage III thyroid carcinoma (T3N0M0)</td>
</tr>
</tbody>
</table>

aClinical interpretations identified 5 additional suspicious areas in 5 individuals that were negative on further radiographic or endoscopic evaluation: 1 each in the gallbladder, pubic area, inguinal nodes, and uterus. One uterine abnormality was found to be a benign fibroid at a previously scheduled hysterectomy.

bScoring system formal review: 1, definitely benign; 2, probably benign; 3, equivocal; 4, probably malignant; 5, definitely malignant.
Upper endoscopy with endoscopic ultrasound identified a stage IIA 3-cm esophageal adenocarcinoma (T3N0M0). He underwent intensive preoperative chemotherapy, radiation followed by surgery, and adjuvant chemotherapy.

No other lesion was scored greater than 2 (probably benign) in the standardized review. Clinical FDG-PET/CT scan interpretations of lesions in 5 patients led to additional images (n=4) or procedures (1 colonoscopy and 1 hysterectomy previously planned for fibroid tumors); all were found to be negative.

COMMENT

Among hereditary cancer predisposition syndromes, LFS has presented special challenges because of the early onset and diverse spectrum of cancers for which carriers have increased risk. The National Comprehensive Cancer Network guidelines (http://www.nccn.org) provide a surveillance program for adults with LFS based on expert opinion and extrapolation from other syndromes. Recommendations include annual comprehensive physical examinations with skin and neurological assessment; colonoscopy every 2 to 5 years; additional organ-targeted surveillance based on family history; and, for adult women, biannual clinical breast examinations, annual mammograms, and breast MRI screening starting at age 20 to 25 years. Definitive data are often unavailable for rare syndromes, which are hampered by selection and insufficient numbers of individuals to permit randomized designs.

In this pilot study, we tested the feasibility of using FDG-PET/CT scanning, a whole-body imaging technique, for this group of individuals who are at increased risk of developing tumors throughout the entire body. The FDG-PET/CT allows the simultaneous acquisition of information on increased glycolytic/metabolic activity in cells and organs (FDG-PET) combined with anatomical references (CT). The FDG-PET/CT has shown accuracy in detecting numerous primary cancers and their metastases including sarcomas, lymphomas, melanomas, and diverse adenocarcinomas and has been used to evaluate nearly all tumors associated with LFS. For example, FDG-PET/CT scans have shown a greater than 70% sensitivity in detecting sarcomas and brain tumors, both hallmarks of LFS. There have been few reports of PET/CT as a cancer screening tool.

We performed a blinded central review of the FDG-PET/CT images of our cohort of 15 individuals and identified lesions that were characterized as likely, and later confirmed to be malignant, in 3 (20%). All 3 individuals were able to undergo potentially curative treatments. Clinical review led to additional procedures in one-third of individuals, which has important im-

Figure 1. Fluorodeoxyglucose F18–Positron Emission Tomography/Computed Tomography (FDG-PET/CT) Images of an Individual With a Thyroid Cancer

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applications for subsequent study design. There have been no malignancies detected in the brief clinical follow-up of these patients (median, 8.5 months). The results of this pilot study are encouraging in this patient population given that treatable malignancies were detected in 20% of patients. A larger trial is needed to properly evaluate the clinical benefit and diagnostic performance of the screening in terms of sensitivity, specificity, and observer variability. The routine clinical use of FDG-PET/CT for screening patients with LFS may be less effective than in this controlled setting.

Imaging with FDG-PET/CT provides the opportunity to explore the whole body noninvasively. However, any radiation exposure should be carefully considered because individuals with LFS are at increased risk of subsequent primary malignant tumors. The radiation exposure from the single FDG-PET/CT scan performed in this trial (approximately 2.4 rem) is about equivalent to the sum of clinical chest, abdomen, pelvis, and head CT scans, and half the annual exposure limit for radiation workers. It is considered acceptable for currently approved clinical indications, which do not include screening, particularly in radiation-sensitive populations. Radiation doses from diagnostic procedures are typically 2 to 3 orders of magnitude smaller than the dose of therapeutic radiation with which secondary cancers have been linked. Nevertheless, there is growing concern for potential radiation risks of diagnostic procedures such as CT scans, particularly in the general population.

While the purpose of this study was to evaluate LFS screening with optimal FDG-PET image quality, the injected FDG dose could be reduced and the CT technique adjusted to include longer acquisitions, manual specification, or newer CT scanners with increased sensitivity without sacrificing quality. A more definitive clinical trial evaluating FDG-PET/CT scanning in this population also should consider the appropriate scanning interval, age at initiation of screening, and possible alternate non–radiation-dependent techniques.

This study has several limitations. Because of the rarity of LFS, our sample size in this pilot study is small, and our convenience sample included cancer survivors free of disease for 5 years or more. The scans are incident, so they are more likely to identify prevalent occult disease. We identified a gastroesophageal junction tumor before it became symptomatic, but do not know whether this discovery will contribute to the patient’s survival. Papillary thyroid cancers in individuals without LFS are often associated with very long survival; any potential differences in be-

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**Figure 2.** Fluorodeoxyglucose F18–Positron Emission Tomography/Computed Tomography (FDG-PET/CT) Images of an Individual With a Gastroesophageal Junction Cancer

Whole-body maximal intensity projection image (left) and axial transverse slices through the gastroesophageal junction displayed as PET (top right), CT (middle right), and fused PET/CT images (bottom right) of a patient with Li-Fraumeni syndrome showing focal FDG uptake in the gastroesophageal region. The spiral CT scan was performed with a moderate dose to enable anatomical localization in addition to correction of photon attenuation. Arrowheads indicate location of adenocarcinoma at the gastroesophageal junction.
behavior have not been evaluated in patients with LFS.

In conclusion, FDG-PET/CT imaging has the potential to detect a wide variety of cancers at potentially curable stages. The use of an imaging technique that is effective in detecting cancer in the whole body with acceptable radiation exposure could potentially be considered for the screening of high-risk groups, such as LFS families, if confirmed in a larger study.

Author Contributions: Dr Garber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES