Prevalence of Cancer at Baseline Screening in the National Cancer Institute Li-Fraumeni Syndrome Cohort

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Importance Establishment of an optimal cancer surveillance program is important to reduce cancer-related morbidity and mortality in individuals with Li-Fraumeni syndrome, a rare, highly penetrant cancer predisposition syndrome.

Objective To determine the feasibility and efficacy of a comprehensive cancer screening regimen in Li-Fraumeni syndrome, using multiple radiologic techniques, including rapid whole-body magnetic resonance imaging (MRI) and laboratory measurements.

Design, Setting, and Participants Baseline evaluation of a prospective cancer screening study was conducted from June 1, 2012, to July 30, 2016, at the National Cancer Institute, National Institutes of Health (an academic research facility). Participants included 116 individuals with Li-Fraumeni syndrome with a germline TP53 pathogenic variant who were aged 3 years or older at the time of baseline screening and had not received active cancer therapy at least 6 months prior to screening.

Main Outcomes and Measures Detection of prevalent cancer with multimodal screening techniques and the need for additional evaluation.

Results Of the 116 study participants, 77 (66.4%) were female; median age was 37.6 years (range, 3-68 years). Baseline cancer screening led to the diagnosis of cancer in 8 (6.9%) individuals (2 lung adenocarcinomas, 1 osteosarcoma, 1 sarcoma, 1 astrocytoma, 1 low-grade glioma, and 2 preinvasive breast cancers [ductal carcinoma in situ]); all but 1 required only resection for definitive treatment. A total of 40 (34.5%) participants required additional studies to further investigate abnormalities identified on screening, with 32 having incidental, benign, or normal findings, resulting in a false-positive rate of 29.6%. Non-MRI techniques, including baseline blood tests, abdominal ultrasonography in children, mammography, and colonoscopy, did not lead to a diagnosis of prevalent cancer in our cohort.

Conclusions and Relevance This study describes the establishment and feasibility of an intensive cancer surveillance protocol for individuals with Li-Fraumeni syndrome. Prevalent cancers were detected at an early stage with baseline whole-body, brain, and breast MRI. Prospective screening of the participants is under way.

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i-Fraumeni syndrome (LFS) (TP53; OMIM *191170) is an autosomal-dominant cancer predisposition syndrome characterized by early-onset cancers and a high lifetime cancer risk.1 The most common LFS-associated cancers are premenopausal breast cancer, osteosarcoma, soft-tissue sarcomas, brain tumors, leukemia, and adrenocortical carcinoma.2-4 Germline pathogenic variants in TP53 were recognized to be the underlying molecular basis of LFS in 1990 and are identified in approximately 70% of families meeting the clinical diagnostic criteria of classic LFS.5,6 With increasing numbers of individuals with TP53 mutations identified through wider access to and broader scope of genetic testing, the LFS cancer spectrum has expanded to include melanoma, lung, gastrointestinal tract, thyroid, and ovarian cancers.4,7-9 The cumulative cancer risk in LFS has been estimated to be approximately 50% by age 40 years and up to 90% by age 60 years,10 with females having a higher risk than males, largely due to the occurrence of premenopausal breast cancer.11-14 Individuals with LFS also have a substantial lifetime risk of subsequent cancers, which necessitates continued cancer surveillance.4,9,13-15

The early detection of cancer has the potential to reduce morbidity and mortality in individuals with LFS, and identification of the optimal screening regimen is an area of active investigation. Two studies using 18 F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-PET/CT) scans for cancer surveillance reported that 10% to 20% of asymptomatic participants with LFS were found to have cancers at baseline screening.16,17 However, the radiation exposure associated with PET/CT imaging (12-15 millisieverts) has limited the applicability of PET/CT scanning as a screening technique. Rapid whole-body (WB) magnetic resonance imaging (MRI) has been used for cancer diagnosis and staging,18 as well as for cancer surveillance, in a number of cancer predisposition syndromes.19-22 To date, 1 study has reported on a comprehensive cancer surveillance strategy using rapid WB MRI and other cancer-screening modalities in 89 adults and children with germline TP53 mutations.23,24 Individuals who underwent cancer surveillance had significantly lower cancer-related mortality and higher overall survival compared with those who did not, suggesting that a comprehensive surveillance strategy is feasible and clinically relevant.24 Based, in part, on these data, the current guidelines recommended by the National Comprehensive Cancer Network include screening for breast cancer with annual breast MRI and/or mammography, based on age, annual rapid WB MRI with or without a separate brain MRI, colonoscopy every 2 to 5 years, annual dermatologic examination, and additional targeted surveillance based on family history of cancer.25

To further understanding of cancer screening in individuals with LFS, we are conducting a longitudinal, comprehensive cancer screening study, using WB MRI, brain and breast MRIs, mammogram, colonoscopy, abdominal ultrasonography, and blood tests for individuals with germline TP53 mutations. Herein, we report on the prevalence of cancer and incidental findings identified at the baseline screening evaluation.

Methods

Study Participants

Participants in the present study are enrolled in a National Cancer Institute long-term, prospective cohort study on LFS that opened to accrual in August 2011, with cancer screening starting in June 2012.26 A detailed description of the study was reported elsewhere.14,27 Study participants were eligible to undergo protocol-defined cancer screening if they tested positive for a germline TP53 pathogenic variant and were older than 3 years at screening (Table 1 in the Supplement). The lower age limit of 3 years was chosen based on the available expertise and resources at the National Institutes of Health (NIH) Clinical Center. Participants with a prior cancer diagnosis were eligible for the screening protocol if they had completed therapy (chemotherapy and/or radiotherapy, with the exception of adjuvant hormone therapy for breast cancer) 6 months or longer before screening. If the prior cancer was treated with curative surgery only, participants were eligible for screening after recovery from surgery.

The study was approved by the National Cancer Institute Institutional Review Board. Written informed consent was obtained from all participants or from the parents if the participant was younger than 18 years. A study assent was obtained from children aged 13 to 18 years. The participants did not receive financial compensation.

Cancer Screening Protocol

Participants were evaluated and underwent screening examinations at the NIH Clinical Center in Bethesda, Maryland. The cancer screening protocol was designed based on a previously published study on LFS23 and is shown in the Box. Preliminary data from that study showed promise in detecting cancers at early stages and reducing mortality. We aimed to evaluate the screening protocol in a larger population and adapted the protocol with a few modifications. First, in the pediatric population, ultrasonography screening for adrenocortical carcinoma was performed every 4 months.
Children (Aged 3-16 Years)
- Annual complete history and physical examination
- Blood tests every 4 months: complete blood cell count with differential, lactate dehydrogenase, erythrocyte sedimentation rate, β-human chorionic gonadotropin, α-fetoprotein, 17-hydroxyprogesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione
- Abdominal ultrasonography every 4 months
- Annual brain MRI
- Annual rapid whole-body MRI

Children Older Than 16 Years and Adults
- Annual history and physical examination
- Blood tests every 4 months: complete blood cell count with differential, lactate dehydrogenase, erythrocyte sedimentation rate
- Annual brain MRI
- Annual rapid whole-body MRI
- Colonoscopy every 3 years, starting at 25 years*
- Females
  - 20-40 years: annual breast MRI, mammography optional
  - >40 years: annual breast MRI and mammography

Abbreviation: MRI, magnetic resonance imaging.
* Colonoscopy not required at baseline if done within 1 year of baseline screening visit.

Box. Cancer Screening Regimen

instead of every 3 to 4 months, for logistical reasons. Second, complete urinalysis was eliminated since it is not specific. Third, in the adult population, clinical breast examination was done annually instead of twice a year. Most of our study participants travel to the NIH Clinical Center from out of state, and it is not feasible to have them return for a clinical breast examination at 6 months. Fourth, mammography performed between ages 20 and 40 years was optional. We weighed the benefits and the potential risks of and cumulative radiation exposure from mammograms in younger women and, because there were insufficient data to demonstrate that the benefits clearly outweigh the risks, we decided to make mammograms optional for this age group. Finally, colonoscopy was performed every 3 to 5 years starting at age 25 years, which was modified from National Comprehensive Cancer Network recommendations for colorectal cancer screening in cancer-prone populations of every 2 years starting at 40 years. The WB MRI was performed with and without gadolinium contrast; details are described in the eAppendix and eTable 2 in the Supplement. The annual cancer screening visit to the NIH Clinical Center included the WB MRI, brain MRI, bilateral breast MRI, blood tests, and abdominal ultrasonography. Participants had the option of undergoing other screening studies (interim blood tests, abdominal ultrasonography, annual mammography, and colonoscopy) performed at their local health care institution. Additional radiologic imaging and procedures were performed as clinically indicated to follow up on the results of the screening examinations.

Demographics and previous cancer history were obtained on all participants at the baseline screening visit and by extensive medical records review. Statistical analyses were performed on Microsoft Excel, version 16.0 (Microsoft Corp).

Results

A total of 116 TP53 mutation-positive participants, 39 (33.6%) males and 77 (66.4%) females, from 60 families underwent baseline cancer screening between June 1, 2012, and July 30, 2016; the number of participants per family ranged from 1 to 10. The majority (96%) of the participants self-identified as white and the others were of mixed races. There were 96 adults and 20 children, with median age of 37.6 years (range, 3-68 years). Seventy-one of 116 (61.2%) of screening participants had a history of at least 1 cancer diagnosis prior to their baseline screen (range, 1-9 cancers). The types and number of previous cancer diagnoses are reported in eTable 3 in the Supplement, and more than 90% were confirmed by review of pathology and/or physician report. Among the participants with a previous cancer history, the median age at diagnosis was 28 years (range, 6 months to 61 years), and the median interval between the most recent cancer diagnosis and baseline screening was 3.8 years (range, 4 months to 54 years).

Whole-Body MRI

Abnormal MRI findings requiring additional follow-up were identified in 32 of the 116 WB MRIs (27.5%) performed, including 1 brain mass seen on both WB MRI and brain MRI. Further evaluation included additional imaging studies, close clinical monitoring, and/or site-specific biopsy. Twenty-seven of 32 (84.4%) of the abnormal WB MRIs required follow-up, including 2 site-specific biopsies, with results showing benign or normal findings (eTable 4 in the Supplement).

Five cancers were diagnosed in the 32 individuals (15.6%) with abnormal WB MRI findings, which is 4.3% of the total screening cohort (eTable 4 in the Supplement). Two of the cancers diagnosed were asymptomatic lung adenocarcinomas:stage IB in a woman in her 40s and stage IA in a woman in her 60s (eFigure, A and B in the Supplement). Both cancers were completely resected and required no additional therapy. Follow-up MRI and biopsy of a posterior left fourth rib lesion showed an intermediate-grade osteosarcoma in a man in his 20s with no history of cancer (eFigure, C in the Supplement). He underwent resection, followed by 6 cycles of chemotherapy, including methotrexate sodium, doxorubicin hydrochloride, and cisplatin, a result of positive surgical margins. Follow-up imaging 1 month after completion of chemotherapy showed recurrent disease in the fifth rib and the body of the T5 vertebra. At the time of the study, he was receiving chemotherapy with ifosfamide and etoposide, with good radiologic response at last contact. Biopsy of a 0.6-cm, left chest skin-based lesion in an asymptomatic woman in her 40s showed a low-grade spindle cell sarcoma, possibly related to the radiotherapy she received for infiltrating ductal carcinoma of the left breast 3 years earlier (eFigure, D in the Supplement). The fifth cancer was a brain tumor detected both by brain MRI and WB MRI and is detailed below.
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Brain MRI
Five of 116 baseline brain MRIs (4.3%) required additional evaluation, which led to the diagnosis of 2 cancers. Baseline brain MRI in an asymptomatic teenaged girl showed a 5-cm right frontal mass (eFigure, E in the Supplement). This mass was also noted on her WB MRI. She underwent a gross total resection of the mass, which showed a World Health Organization grade II astrocytoma, with no adjuvant therapy indicated. The brain MRI of a woman in her 20s with a history of bilateral breast cancer 2 years earlier showed a 0.5-cm lesion in the left thalamus. Biopsy of the lesion was consistent with a low-grade glioma. Based on the location and pathologic features of the glioma, close radiologic monitoring with quarterly brain MRI was recommended. Three additional follow-up studies were indicated in 3 patients, including a neck MRI, a 6-month follow-up brain MRI for a small cystic lesion in the right periventricular white matter, and an evaluation for an inflammatory demyelinating process, including additional brain imaging and cerebrospinal studies, which led to the diagnosis of multiple sclerosis in an asymptomatic woman in her 30s (eTable 4 in the Supplement).

Breast MRI
A total of 22 female participants, aged 22 to 65 years, had baseline screening bilateral breast MRI. Four of the 22 (18.2%) participants required additional evaluation owing to abnormalities noted on breast MRI. Of these, 2 resulted in a diagnosis of ductal carcinoma in situ (eFigure, F in the Supplement). One participant underwent bilateral mastectomy, and 1 woman had lumpectomy followed by adjuvant hormonal therapy with tamoxifen. One participant underwent a follow-up breast MRI that showed a stable nodule. Evaluation of the fourth abnormality showed a benign-appearing breast cyst (eTable 4 in the Supplement).

Non-MRI Screening
Eight protocol-defined baseline screening mammograms were performed, none of which detected any abnormalities. Of the 2 women with ductal carcinoma in situ diagnosed by breast MRI, 1 had a normal mammogram 6 months prior to baseline breast MRI and 1 had not had a baseline mammogram prior to the breast MRI that led to the diagnosis of ductal carcinoma in situ.

A total of 39 baseline colonoscopies were performed (defined as performed within 1 year of the screening visit to the NIH Clinical Center). None required additional follow-up, and no malignant tumors were diagnosed.

None of the 116 baseline blood tests and 20 baseline abdominal ultrasonography examinations performed in children showed significant abnormalities concerning for cancer, and none required additional evaluation.

Discussion
In this study of a comprehensive cancer surveillance strategy for individuals with germline pathogenic variants in TP53, we report a cancer detection rate of 6.9% at baseline screening among 116 individuals. Of the 8 prevalent cancers diagnosed, 4 were detected by WB MRI alone (4 of 116 [3.4%]); 2 by brain MRI (2 of 116 [1.7%]), 1 of which was also seen on WB MRI; and 2 by breast MRI (2 of 22 [9.1%]). Only 1 of the 8 cancers diagnosed required chemotherapy.

The 6.9% detection rate of prevalent cancer in this cohort of patients is slightly lower than the 10.0% (3 cancers in 30 individuals) reported by Nogueira et al16 and the 20.0% (3 cancers in 15 individuals) previously reported in baseline screening with FDG-PET/CT in individuals with LFS.17 The reports of Villani et al,23,24 on which our screening strategy was based, did not explicitly state the number of cancers at the first cancer screening visit; thus, we cannot make a direct comparison of the data. Regardless, differences in cancer detection rates may be partially explained by variations in demographic characteristics and history of cancer, and thus, different cancer risk level at screening between our study population and the previously reported studies.9,14

We defined a false-positive screening test as any radiologic or laboratory finding that necessitated additional specific evaluation in the individuals who did not have cancer. Forty of the 116 participants (34.5%) underwent additional evaluation, 8 of whom were diagnosed with cancer, resulting in a false-positive rate of screening of 29.6% (32 of 108 individuals without cancer). As expected, most of the radiologic abnormalities requiring additional follow-up were seen with WB MRI, with a false-positive rate of 25.0% (27 of 108). This finding includes the detection of benign entities, such as enchondroma and nonossifying fibroma, and anatomic variants, such as congenital foregut duplication cyst. With prospective screening and subsequent annual follow-up scans, the false-positive rate of WB MRI is expected to decrease over time, as the known benign findings or anatomic variants would not need to be further evaluated. Paradoxically, with advances in imaging technologies and improvements in MRI scan quality, the rate of false-positive findings could potentially increase over time. For example, at the beginning of the study, lung detail was poorly identified on WB MRI. Ever-increasing quality of MRI scans has resulted in reduced motion artifacts, so that underlying anatomic details are now revealed. Unfortunately, some MRI features in the lung, bone, and abdomen have nonspecific etiology and will usually require further evaluation. The pretest probability of cancer in individuals with LFS is relatively high, but this finding should be balanced with the understanding that WB MRI is subject to many artifacts from motion and magnetic field inhomogeneity that can simulate disease, particularly in the abdomen.

An essential aspect of cancer surveillance is the psychosocial effect of an intense screening regimen, such as those proposed for LFS and reported on here. In our study, we did not detect objective evidence of unexpected psychological distress at the time of baseline screening in a subset of participants.27 However, the effect of regular and long-term cancer surveillance and additional testing burden for follow-up evaluation in LFS is unknown. In a study conducted in the Netherlands evaluating the adherence to recommendations for cancer screening, the perceived risk and benefits of screening, and the associated levels of distress and
worry in a population of individuals with TP53 mutations or at 50% risk of having a mutation, most participants reported perceived benefits of screening, with no evidence of significant levels of distress. While the proactive approach of undergoing cancer surveillance may offer a sense of empowerment, screening may also cause stress from waiting for results, and the emotional burden of additional follow-up testing is unknown. The prospective analysis of psychosocial consequences of screening, cancer worry, and emotional distress are under way.

**Strengths and Limitations**

Our study confirms the feasibility of an intensive cancer screening protocol for individuals with LFS. The strengths of our study include its relatively large number of participants, with a wide age range inclusive of young children and older adults. All baseline WB MRIs, all but 2 brain MRIs, and all but 1 bilateral breast MRI were performed at the NIH Clinical Center. This setting allows for MRI examination and interpretation consistency, as well as direct comparison of prior imaging test results. A limitation of our study is that, since most of the imaging studies were performed at the NIH Clinical Center, many participants traveled from across the country for screening, necessitating days absent from work and/or school.

**Conclusions**

This comprehensive cancer screening regimen for children and adults with TP53 mutations is feasible and shows a prevalent cancer detection rate of 6.9% at the baseline screen. All of the prevalent cancers were detected by MRI. Although no prevalent cancers were identified by colonoscopy, mammography, or bloodwork at baseline screening, we are not able to evaluate the value that these modalities contribute to a prospective, comprehensive surveillance protocol. Our screening study is ongoing, and we plan to evaluate the efficacy of MRIs and non-MRI screening tools in the detection of incidence cancers in the future. Our data suggest that comprehensive cancer screening should be offered to all individuals with germline TP53 mutations. A number of institutions are investigating the use of WB MRI as a cancer screening modality in LFS. Their anticipated results, along with additional data from longer follow-up of our study, will provide much-needed information required to establish a screening regimen that might lead to a reduction in cancer-related morbidity and mortality for individuals with LFS. With additional data, we will be able to more comprehensively evaluate the performance characteristics of the screening regimen and its effect on long-term outcomes, as well as the feasibility of the regimen over a long period.

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Original Investigation Research

Cancer Screening in Li-Fraumeni Syndrome

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Li-Fraumeni syndrome is a highly penetrant cancer predisposition syndrome that is being more frequently detected because of increased awareness and genetic testing for germ-line mutations in the TP53 tumor suppressor gene (OMIM *191170). Management of individuals with Li-Fraumeni syndrome is one of modern medicine's most challenging dilemmas. How do we alter the natural history associated with a known genetic lesion? The lifetime probability of cancer in those with Li-Fraumeni syndrome is nearly 100% in women and 80% in men, and thus cancer screening may seem appealing for earlier detection and management. Nevertheless, the complexities of this syndrome may limit the effectiveness of screening. The diverse spectrum of cancers would require an exhaustive screening program, and the aggressiveness of some of the cancers may justify short intervals between examinations. Whole-body magnetic resonance imaging (MRI) offers an attractive radiation-free imaging option with a high resolution for many of the Li-Fraumeni-spectrum tumors. In this issue of JAMA Oncology, the results of 2 important studies1,2 are presented on the use of whole-body MRI as a cancer screening technique in Li-Fraumeni syndrome.

Ballinger et al1 used meta-analytic methods to estimate the performance and frequency of cancer detection of whole-body MRI used at baseline. Data were collected through the Li-Fraumeni Exploration Research Consortium with data contributors from North America, Europe, Brazil, and Australia. Data on 578 patients were compiled, which is a large number considering the rarity of the syndrome. Baseline whole-body MRI resulted in the detection of 225 lesions that required further follow-up, of which 42 malignant neoplasms were confirmed by other imaging techniques and biopsy. Consequently, 7% of individuals who underwent MRI were found to have cancer, but this detection frequency is offset by a false-positive rate of 43% and the range of cancers detected, which were mostly early-stage tumors. Three important sources of heterogeneity were investigated. Sex and country did not seem to change the detection rate, but the detection rate in children was modestly higher than in adults.

Mai et al2 reported baseline screening results from the National Cancer Institute (NCI) Li-Fraumeni syndrome cohort, which was also included as part of the meta-analysis by Ballinger et al.1 This cohort included 116 individuals, the largest cohort of individuals with Li-Fraumeni syndrome to date. The screening protocol included yearly whole-body MRI and blood tests every 4 months for all individuals, additional abdominal ultrasonography every 4 months for children, and dedicated breast and brain MRI and colonoscopy for adults. From the baseline screening, 8 cancers were detected, with the most aggressive being osteosarcoma. Whole-body MRI detected most of the cancers but was also associated with a substantial proportion of false-positive findings (25%). No significant abnormalities were detected in the blood samples, which supports recently published recommendations to refrain from using blood sampling as part of a screening program.3 Longitudinal analyses of these data will be of substantial interest. A plausible assumption is that information from previous scans and results may be used to lower the proportion of false positives.

These studies illustrate that the detection of early resectable cancer is possible in Li-Fraumeni syndrome, but several limitations in the evidence need to be addressed before intensive screening protocols and whole-body MRI can be generally recommended. False positives and cancer overdiagnosis may result in psychological distress, radiation exposure from further diagnostic workup, and the risks of unnecessary biopsies and surgery. The risks and benefits of this screening

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Li-Fraumeni syndrome

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