

Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: a prospective observational study



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Summary

Background Individuals with Li-Fraumeni syndrome have a high lifetime risk of developing cancer. We assessed the feasibility and potential clinical effect of a comprehensive surveillance protocol in asymptomatic *TP53* mutation carriers in families with this syndrome.

Methods We implemented a clinical surveillance protocol, using frequent biochemical and imaging studies, for asymptomatic *TP53* mutation carriers on Jan 1, 2004, and did a prospective observational study of members of eight families with Li-Fraumeni syndrome who either chose to undergo surveillance or chose not to undergo surveillance. The primary outcome measure was detection of new cancers. The secondary outcome measure was overall survival.

Findings As of Nov 1, 2010, 33 *TP53* mutation carriers were identified, 18 of whom underwent surveillance. The surveillance protocol detected ten asymptomatic tumours in seven patients, including small, high-grade tumours and low-grade or premalignant tumours. All seven mutation carriers were alive after a median follow-up of 24 months (IQR 22–65 months). 12 high-grade, high-stage tumours developed in 10 individuals in the non-surveillance group, two of whom (20%) were alive at the end of follow-up ($p=0.0417$ for comparison with survival in the surveillance group). 3-year overall survival was 100% in the surveillance group and 21% (95% CI 4–48%) in the non-surveillance group ($p=0.0155$).

Interpretation Our findings show the feasibility of a clinical surveillance protocol for the detection of asymptomatic neoplasms in individuals with germline *TP53* mutations. This strategy offers a management option for affected individuals, and its benefits lend support to the use of early genetic testing of at-risk individuals and families.

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Introduction

Characterisation of heritable germline mutations in tumour suppressor genes or oncogenes offers the potential for genetic screening, with the goal of prevention, early detection, and improved prognosis for patients with inherited cancer susceptibility.

Li-Fraumeni syndrome is an autosomal dominantly inherited prototypic cancer predisposition syndrome characterised by a high frequency of soft tissue sarcomas, osteosarcomas, premenopausal breast cancer, brain tumours, adrenocortical carcinoma, leukaemia, and other malignant diseases, which typically occur at an earlier age in affected individuals than in the general population.^{1,2}

The classic definition of Li-Fraumeni syndrome is an index patient (proband) with a sarcoma diagnosed before 45 years of age, who has a first-degree relative younger than 45 years of age with any cancer, and a first-degree or second-degree relative with any cancer before the age of 45 years or a sarcoma at any age.³ Less stringent criteria have been referred to as Li-Fraumeni-like syndrome.^{4–6} Constitutional mutations of the *TP53* tumour suppressor gene are the primary underlying genetic alteration that predisposes individuals to the

development of cancer.^{7,8} Germline *TP53* mutations occur in 70–83% of patients who meet the classic Li-Fraumeni syndrome criteria^{9,10} and 29–35% of patients who meet the updated Chompret criteria.^{6,11,12}

In *TP53* mutation carriers, the lifetime risk of developing cancer has been estimated to be as high as 73% for male carriers, and 93% for female carriers.¹³ In view of these striking cancer risks, close surveillance of affected individuals to enable early detection of neoplasms and improve clinical outcomes seems imperative. However, the diverse range of tumours, variability of age at onset, generally weak *TP53* mutation genotype–phenotype correlations, and absence of evidence for effectiveness of screening have largely discouraged this practice.^{14–17}

Clinical surveillance strategies have been established and successfully implemented for several cancer susceptibility syndromes.¹⁷ On the basis of available data, our own experience with these disorders, and detection strategies for patients with sporadic Li-Fraumeni syndrome component tumours,^{18–20} we developed a practical surveillance protocol that uses non-invasive biochemical and imaging modalities for the management of patients with this syndrome. Here

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we show the feasibility and potential clinical benefits of such a protocol.

Methods

Patients and study design

The protocol was implemented at The Hospital for Sick Children (Toronto, ON, Canada) on Jan 1, 2004, and has been adopted in several institutions across North America.

We assessed eight families with Li-Fraumeni syndrome from whom sufficient clinical and molecular information was available. Patients were recruited from three centres: the Cancer Genetics Program at The Hospital for Sick Children, Division of Hematology/Oncology at Children's Hospital of Los Angeles (CA, USA), and Primary Children's Medical Center and the Family Cancer Assessment Clinic at Huntsman Cancer Institute at the University of Utah (Salt Lake City, UT, USA). All families underwent comprehensive genetic counselling before and after *TP53* mutation analysis. All germline *TP53* mutation carriers were offered participation in the surveillance protocol (panel 1), and the purpose and potential risks of each test were outlined. Individuals then opted either to undergo surveillance or not, and were thereafter divided into surveillance and non-surveillance groups and followed up prospectively.

TP53 mutation analysis was done in the clinical molecular diagnostic laboratories at The Hospital for Sick Children in Toronto or through the Primary Children's Medical Center at Huntsman Cancer Institute, University of Utah. Sequencing of exons 2–11 including at least 50 bases into introns was done, in addition to multiplex ligation-dependent probe amplification analysis of gene copy number. Complete family histories, including site and age at diagnosis of neoplasms, were obtained with follow-up history during routine clinic visits to document new cancer diagnoses in family members. Diagnoses were confirmed by review of relevant pathology reports. In addition to the *TP53* mutation carriers identified since 2004 and offered participation in the protocol, affected relatives who were not genotyped, but who were deemed obligate *TP53* mutation carriers by being in the direct parental lineage of the *TP53* mutation carrier proband were also identified and included in a secondary analysis (historical group). During the study, all patients were treated in line with the standard of care at their respective institutions for their specific tumour, irrespective of their *TP53* status.

Written informed consent was obtained from all adult family members, and children older than the age of consent in their respective jurisdictions. Parents provided written informed consent for children younger than the age of consent. The research testing for the study was approved by research ethics boards at the participating institutions and the clinical surveillance protocol was approved in each participating institution.

Statistical analysis

The number of survivors (individual mutation carriers) in the surveillance and non-surveillance groups were compared with stratified exact conditional logistic regression (conditioning on family) to deal with the clustered nature of the binary data (in which a cluster is a family).²¹ Kaplan-Meier curves were created and compared with a stratified log-rank test, in which family groupings were used for stratification. Time-to-event

For the surveillance protocol see <http://www.sickkids.ca/pdfs/Cancer-Genetics-Program/35386-TP53TorontoProtocol.pdf>

For specifications of the rapid total body MRI see <http://www.acrin.org>

Panel 1: Surveillance strategy for individuals with germline *TP53* mutations*

Children

Adrenocortical carcinoma

- Ultrasound of abdomen and pelvis every 3–4 months
- Complete urinalysis every 3–4 months
- Blood tests every 4 months: β -human chorionic gonadotropin, alpha-fetoprotein, 17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid total body MRI

Leukaemia or lymphoma

- Blood test every 4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

Adults

Breast cancer

- Monthly breast self-examination starting at age 18 years
- Clinical breast examination twice a year, starting at age 20–25 years, or 5–10 years before the earliest known breast cancer in the family
- Annual mammography and breast MRI screening starting at age 20–25 years, or at earliest age of onset in the family
- Consider risk-reducing bilateral mastectomy

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid total body MRI
- Ultrasound of abdomen and pelvis every 6 months

Colon cancer

- Colonoscopy every 2 years, beginning at age 40 years, or 10 years before the earliest known colon cancer in the family

Melanoma

- Annual dermatological examination

Leukaemia or lymphoma

- Complete blood count every 4 months
- Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

*In addition to regular assessment with family physician with close attention to any medical concerns or complaints.

was time from diagnosis to death, or time from diagnosis to last follow-up, or to Nov 1, 2010, when the study follow-up finished. The subject of this latter analysis was cancer diagnoses, with each neoplasm counted individually in the analysis for patients with multiple cancers. A family variable was created and assigned the same family designation for measurements from the same family or from the same individual. This newly created variable was then used as a clustering variable in a marginal Cox regression model with a robust sandwich variance estimator.²² The new family variable was used as the identification statement to indicate that observations with the same identification are from the same cluster, and thus correlated. Statistical calculations were done with SAS software (version 9.2).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. AV, UT, JS, JB, JF, and DM had full access to all the data and DM had final responsibility for the decision to submit for publication.

Results

As of Nov 1, 2010, comprehensive clinical and molecular information was available for eight families, giving a total of 48 individual *TP53* mutation carriers. Since the initiation of the surveillance protocol on Jan 1, 2004, *TP53* mutation status was confirmed in 33 of these patients, 18 of whom decided to undergo surveillance and 16 decided not to undergo surveillance (one patient is included in both groups for malignancies diagnosed before and after the onset of surveillance). All patients undergoing surveillance were fully compliant with the protocol in all three participating institutions and no patients withdrew.

The clinical surveillance protocol identified a total of ten neoplasms in seven *TP53* mutation carriers, all of

	No surveillance						Surveillance						
	Tumour type	Sex	Age at diagnosis	Status	Age at death or age at end of follow-up	Follow-up time	Tumour type	Mode of detection	Sex	Age at diagnosis	Status	Age at end of follow-up	Follow-up time
Family one: Arg175His (c.524G>A)													
Patient 1	MB*	M	14.5 years	Dead	15.5 years	13 months
Patient 2	NHL; IDC	F	27; 36 years	Dead	38 years	134; 24 months
Patient 3	AML	F	58 years	Alive (disease free)	76 years	219 months
Patient 4	CA	M	..	Dead
Patient 5	SC	M	20 years	Alive (disease free)	46 years	316 months
Patient 6	BC	F	37 years	Dead
Family two: IVS03-11 C>G													
Patient 1	RMS*	M	3 years	Dead	5 years	19 months
Patient 2	GBM	F	9 years	Dead	9 years	6 months
Patient 3	PD-IDC; IDC	F	25; 27 years	Alive (disease free)	39 years	167; 137 months	MFH*	Total body MRI and CE	F	30 years	Alive (disease free)	39 years	100 months
Patient 4	BC	F	31 years	Dead	36 years	60 months
Patient 5	BC	F	29 years	Dead	30 years	12 months
Patient 6	TC or LC	M	..	Dead
Patient 7	ACC; PD-IDC (bilateral)	F	9; 27 years	Dead	31 years	264; 48 months
Family three: Tyr163Cys (c.488A>G)													
Patient 1	ACC; AA*	F	2.5; 14 years	Alive (disease free)	18 years	188; 57 months	MDS*	CBC	F	17.5 years	Alive (with disease)	18 years	7 months
Family four: Arg158His (c.473G>A)													
Patient 1	CPC*	M	4.5 years	Dead	5 years	10 months
Patient 2	NBL*	M	2 days	Dead	2 weeks	12 days
Patient 3	TA*	CE and US	F	29 years	Alive (disease free)	31 years	22 months
Family five: Arg248Gln (c.743G>A)													
Patient 1	MB*	F	2.6 years	Dead	2.75 years	1 month
Patient 2	OS*	M	15.5 years	Dead	18.5 years	35 months
Patient 3	NBL	M	2 years	Dead	7 years	60 months

(Continues on next page)

No surveillance							Surveillance						
Tumour type	Sex	Age at diagnosis	Status	Age at death or age at end of follow-up	Follow-up time	Tumour type	Mode of detection	Sex	Age at diagnosis	Status	Age at end of follow-up	Follow-up time	
(Continued from previous page)													
Family six: Ser241Tyr (c.721T>A)													
Patient 1	CPC*; AML*	M	1; 3 years	Dead	3.5 years	30; 5 months
Patient 2	CPC and LGG*; ACC*	MRI brain; AUS and ABW	F	4; 7.5 years	Alive (disease free)	8 years	48; 4 months
Family seven: His193Pro (c.578A>C)													
Patient 1	ACC and CPC*	MRI brain, AUS, and ABW	F	1 year	Alive (disease free)	6.5 years	65 months
Family eight: Arg248Trp (c.742C>T)													
Patient 1	BT	M	42 years	Dead	43 years	12 months
Patient 2	MM*; LC*	M	47; 48 years	Alive (treatment ongoing)	50 years	36; 24 months
Patient 3	SC; SC	M	15; 31 years	Dead	39 years	288; 96 months
Patient 4	BC*	F	27 years	Dead	30 years	36 months
Patient 5	ACC; CPP	F	1; 28 years	Alive (disease free)	41 years	478; 154 months
Patient 6	AA; BC	F	21; 23 years	Dead	23 years	24; 6 months
Patient 7	MB	F	6 years	Dead	9 years	36 months
Patient 8	BT	M	1 year	Dead	2 years	12 months
Patient 9	LGG*	MRI brain	M	24 years	Alive (disease free)	26 years	22 months
Patient 10	LGG*	MRI brain	F	11 years	Alive (stable LGG)	13 years	24 months
<p><i>TP53</i> mutation is given for each family (after family number). Data separated by a semicolon are for sequential diagnoses. AA=anaplastic astrocytoma. ACC=adrenocortical carcinoma. AML=acute myeloblastic leukaemia. BC=breast cancer. BT=brain tumour unspecified. CA=cancer of unknown type. CPC=choroid plexus carcinoma. CPP=choroid plexus papilloma. GBM=glioblastoma multiforme. IDC=invasive ductal carcinoma. LC=lung cancer. LGG=low-grade glioma. MB=medulloblastoma. MDS=myelodysplastic syndrome. MFH=malignant fibrous histiocytoma. MM=malignant meningioma. NBL=neuroblastoma. NHL=non-Hodgkin lymphoma. OS=osteosarcoma. PD=Paget's disease. RMS=rhabdomyosarcoma. SC=sarcoma. TA=thyroid adenoma. TC=throat cancer. AUS=abdominal ultrasound. ABW=adrenal bloodwork. CE=clinical examination. US=ultrasound. F=female. M=male. ..=data not available. *Followed up prospectively since 2004.</p>													

Table 1: Clinical details and survival in germline TP53 mutation carriers with cancer in Li-Fraumeni syndrome families

which were asymptomatic at the time of detection (table 1 and table 2). These include five malignant tumours (two choroid plexus carcinomas, two adrenocortical carcinomas, and one malignant fibrous histiocytoma). The protocol also detected five low grade or premalignant lesions including three low-grade gliomas, a thyroid adenoma, and myelodysplastic syndrome (MDS). All nine solid tumours detected in the surveillance group were completely resected and the patients are in complete remission. One patient with MDS is being considered for allogeneic stem-cell transplantation to try to pre-empt leukaemic transformation. All seven TP53 mutation carriers who developed cancers identified by the surveillance protocol are alive after a median follow-up of 24 months (IQR 22–65).

To objectively assess the effect of the surveillance protocol on survival of patients with cancer, we compared survival for individuals who underwent surveillance to their family members with TP53 mutations who did not undergo surveillance since the initiation of the protocol in 2004. Ten of the 16 mutation carriers followed

prospectively since 2004 in the non-surveillance group developed cancer. All cancers presented symptomatically. These include two choroid plexus carcinomas, two medulloblastomas, one rhabdomyosarcoma, one osteosarcoma, one anaplastic astrocytoma, one neuroblastoma, one acute myelogenous leukaemia, one malignant meningioma, one lung carcinoma, and one breast carcinoma. Fewer individuals with cancer in the non-surveillance group survived until the end of follow-up (two of ten [20%]) than did individuals with cancer in the surveillance group (seven of seven [100%]; $p=0.0417$). We recorded a significant survival advantage in patients who received surveillance, with a 3 year overall survival of 100% for individuals in the surveillance group and 21% (95% CI 4–48%) for individuals in the non-surveillance group ($p=0.0155$ in stratified log-rank test; $n=10$ tumours in seven patients vs 12 tumours in 10 patients; figure). Our analysis with the marginal Cox model with a robust sandwich variance estimator also showed increased survival in the surveillance group compared with the non-surveillance group ($p<0.0001$).

The average age of first tumour diagnosis was 16·6 years in the surveillance group, and 12·9 years in the non-surveillance group. In all families, surveillance was initiated after the proband was diagnosed with cancer and presymptomatic *TP53* gene analysis had been done in family members.

A secondary analysis of all 48 *TP53* mutation carriers in the eight families was done, including those whose *TP53* mutation status had been confirmed before comprehensive initiation of the protocol, or in whom a designation of obligate carrier status could be made on the basis of direct parental lineage with the *TP53* mutation carrier (historical group). Of 33 patients in the non-surveillance group, 28 individuals developed a total of 37 tumours. Only six (21%) of these patients survived until the end of follow-up, compared with all seven (100%) patients with tumours in the surveillance group ($p=0\cdot0056$).

To show feasibility and the effect of the surveillance protocol, a narrative of one of the families included in this analysis is presented in the webappendix (p 1).

Discussion

Use of our surveillance protocol enabled the presymptomatic detection of malignancies with readily available and safe biochemical and imaging techniques in germline *TP53* mutation carriers in families with Li-Fraumeni syndrome. Of 18 patients screened, ten asymptomatic tumours were detected in seven patients during a period of 6 years. Detected tumours included small, localised high-grade tumours, some of which are typically fatal, such as choroid plexus carcinoma.²³ Low-grade and premalignant tumours were also detected and managed before potential progression to a more malignant state. In many patients, early tumour detection allowed definitive localised treatment approaches that precluded exposure to systemic treatment or radiation treatment. One sarcoma, a malignant fibrous histiocytoma, and no breast cancers were detected in the surveillance group—the absence of breast cancers was perhaps because most female participants in the surveillance group were younger than the typical age of onset of breast cancer in Li-Fraumeni syndrome. Furthermore, the young age of some individuals in the surveillance group could explain the high frequency of choroid plexus carcinomas and adrenocortical carcinomas (which are typically tumours of infancy and early childhood) and the low frequency of sarcomas. All patients diagnosed with tumours in the surveillance group were alive at the end of follow-up. The suggestion of improved survival in this group of patients undergoing screening led us to compare the outcomes of these patients to family members who had not undergone surveillance. Kaplan-Meier curves show a significant difference in survival between the two groups of patients managed prospectively in the same treatment era (figure).

	Surveillance		No surveillance		Total	Alive (tumour)	Dead (tumour)
	<i>TP53</i> mutation carrier		<i>TP53</i> mutation carrier	<i>TP53</i> mutation presumed carrier			
	Alive (tumour)	Dead					
Family one	N/A	N/A	1	6	7	3 (2)	4 (5)
Family two	3 (1)	0	2	6	8	2 (2)	6 (7)
Family three	1 (1)	0	1	0	1	1 (2)	0
Family four	1 (1)	0	2	0	2	0	2 (2)
Family five	2 (0)	0	3	0	3	0	3 (3)
Family six	2 (3)	0	1	0	1	0	1 (2)
Family seven	1 (2)	0	0	0	0	0	0
Family eight	8 (2)	0	3	8	11	5 (4)	6 (8)
Total	18 (10)	0	33	11 (10)	22 (27)

Data are number of individuals (number of tumours). N/A=not applicable.

Table 2: Tumour development and survival in families with germline *TP53* mutations

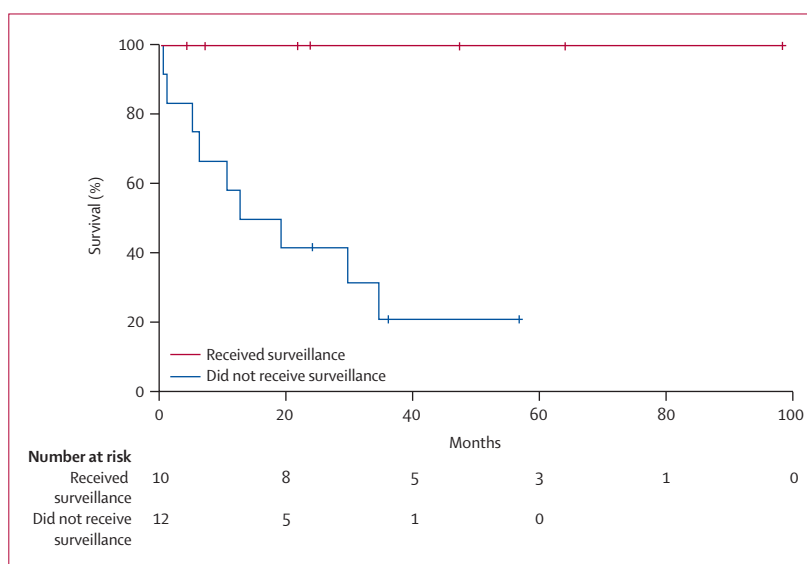


Figure: Survival of *TP53* mutation carriers in surveillance and non-surveillance groups followed prospectively since 2004

n=cancer diagnoses (each neoplasm counted individually for patients with multiple cancers). Curves are marked (+) at the point at which patients were censored.

These findings have implications for the use of predictive genetic screening practices and clinical surveillance strategies, which are discouraged for patients with Li-Fraumeni syndrome because of an absence of evidence of benefit from early detection of malignancies in such individuals.²⁴⁻²⁷ For other cancer predisposition syndromes, including retinoblastoma, multiple endocrine neoplasia, and familial adenomatous polyposis, protocols for presymptomatic genetic testing and surgical prophylactic measures are advocated for, widely accepted, and have shown promise of improved outcomes.^{14,28-30} Some syndromes, including Von Hippel-Lindau disease

See Online for webappendix

and Beckwith-Wiedemann syndrome, have established frequently used protocols for genetic screening and presymptomatic surveillance for early detection. Li-Fraumeni syndrome places *TP53* mutation carriers at risk of developing tumours at any age and in multiple organs. This unpredictable clinical presentation makes development of clinical surveillance strategies more complex than in other syndromes. Nevertheless, on the basis of findings reported here, we argue that genetic screening and presymptomatic surveillance should also be instituted for patients with Li-Fraumeni syndrome who carry the *TP53* mutation.^{14,29}

Of all patients with Li-Fraumeni syndrome, morbidity and loss of life years from malignancies is highest in paediatric patients. Therefore, genetic testing in children deserves special consideration. The American Society of Clinical Oncology recommends consideration of the probability of development of malignancy during childhood when a clinician decides whether to offer genetic testing to potentially affected children, and stresses that all decisions should be made in the child's best interests.¹⁶ Similar recommendations are also made by paediatric advocacy bodies,^{26,31} the National Comprehensive Cancer Network,¹⁷ and the American Society of Human Genetics,²⁴ which cites "timely medical benefit to the child" as primary justification for genetic testing in children. Although the overall risk of cancer is nearly 75% in male and 93% in female carriers of *TP53* mutations, the risk of cancer within the first two decades of life is still high, at an estimated 30–40%.^{1,32} Our data suggest that early detection of neoplasms by surveillance could improve survival, which lends support to the validity of early genetic testing of individuals and, if necessary, their enrolment into a structured surveillance programme. Furthermore, recognition of *TP53* mutation status has implications for treating childhood cancer, because several studies^{3,13,15,33,34} have shown that radiation treatment significantly increases the risk of second malignancies in this group of patients, and thus should be avoided if possible. The hypothesis that germline *TP53* mutations predispose individuals to the risk of radiation-induced carcinogenesis is lent support by studies that document abnormal in-vitro responses of fibroblasts from patients with Li-Fraumeni syndrome to irradiation and chemotherapy.^{35,36}

We advocate for genetic screening in children who are diagnosed with specific component cancers of Li-Fraumeni syndrome, irrespective of family history, especially for adrenocortical carcinomas and choroid plexus carcinomas at any age, rhabdomyosarcomas occurring before 3 years of age, and possibly early onset osteosarcomas (before 10 years of age), because we and others have documented a 50–100% rate of germline *TP53* mutations in these groups.^{6,12} This finding is consistent with other recommendations, most notably from the French Li-Fraumeni syndrome consortium.⁶

Many psychosocial risks are involved in the acquisition of genetic information,^{24,26} as has been explored specifically in patients with Li-Fraumeni syndrome.³⁷ Potential benefits of genetic testing include the emotional relief regarding risk to self and future offspring, and the avoidance of unnecessary medical interventions if a definitive negative test result is obtained.^{16,24} A positive genetic test, however, gives the opportunity for surveillance, for alerting other family members at possible risk, and for making informed family-planning decisions. However, risks exist with surveillance methods, including those associated with anaesthesia for young children undergoing MRI. Furthermore, the possibility of burnout in patients with cancer susceptibility syndromes undergoing lifetime surveillance should be raised and addressed. Although we have not encountered this issue in our cohort of screened patients, the follow-up period might still be too short. Continuous attention to participants by an engaged multidisciplinary team can increase the likelihood of adherence to the protocol. These factors should be considered in the implementation of genetic screening programmes and broad-ranging surveillance for at-risk patients and families.

Few studies have reported findings related to surveillance of families with Li-Fraumeni syndrome. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET and CT screening has been used in one study of patients with Li-Fraumeni syndrome,³⁸ and identified asymptomatic benign and malignant tumours in 20% of patients. However, concerns about radiation exposure in this population could hamper the wider application of this surveillance method. Indeed, because a risk exists of breast tumour induction from radiation exposure of repeated routine mammography in *TP53* mutation carriers,³⁹ advances in non-radiation imaging screening modalities could be applied to future refinements of the surveillance protocol used in this study, by completely replacing mammography with MRI screening. Furthermore, the study that used ¹⁸F-FDG PET and CT screening did not address the feasibility of presymptomatic genetic testing or clinical surveillance strategies in children, nor did it record a survival advantage. The National Comprehensive Cancer Network clinical practice guidelines¹⁷ for individuals with Li-Fraumeni syndrome provide similar recommendations for breast cancer surveillance, whereas our protocol is more detailed and prescriptive for detection of other component tumours of Li-Fraumeni syndrome.

Finally, although the early detection of an asymptomatic adrenocortical carcinoma in a 5-year-old girl with Li-Fraumeni syndrome by use of a surveillance strategy similar to our own has been reported,⁴⁰ our findings show the effectiveness and feasibility of surveillance in varying genetic, oncological, and health-delivery practice patterns. None of our patients have encountered barriers to completing various clinical

surveillance methods, irrespective of the health-care jurisdiction in which they live.

To our knowledge, this study is the first to report the feasibility and potential survival effect of a comprehensive surveillance strategy in patients with Li-Fraumeni syndrome (panel 2). An argument can also be made for continuous surveillance, notwithstanding successful treatment of an identified malignancy, in view of the high likelihood of multiple cancers in this population.^{3,13,15} Furthermore, surveillance could be offered and implemented in the neonatal period or early infancy when mutations are detected prenatally or postnatally, as was done for two patients in this study (one in family two and the other in family four). Additionally, in the future, implementation of a similar protocol in families with Li-Fraumeni-like syndrome in whom a *TP53* mutation is not identified could be considered.

Our study had several possible limitations. The improved survival in the surveillance group could be a product of specific biases. As in other screening studies,^{28,29,30} the propensity of more aggressive tumours to grow rapidly and present with symptoms could account for poorer survival in the non-surveillance group, because these tumours can be more difficult to treat. Also, possible bias from self-selection into groups could have affected the results. Additionally, restricted access to medical facilities might have affected the care of some individuals in the non-surveillance group. Those followed up regularly in a comprehensive cancer genetics clinic through participation in the surveillance protocol could have had more assistance in attending regular appointments and assessments. However, we are not aware that the individuals in the non-surveillance group had otherwise restricted access to medical care.

Another potential bias could have arisen if a discrepancy in ages between the two groups existed. Individuals in the surveillance group could have been mostly children with tumours characteristic of the Li-Fraumeni-syndrome spectrum that were easier to detect and responded better to treatment than those of adults. However, the mean age in each group was similar and we therefore do not think that this factor would affect our findings.

Furthermore, the incorporation of historical patients in the non-surveillance group could account for some of the differences in survival, because less-effective treatment protocols could have been in use at the time of their diagnosis, and their unknown *TP53* status and cancer risk might have delayed presentation for assessment of new symptoms. Additionally, follow-up was longer in the non-surveillance group. To circumvent the potential bias introduced by the incorporation of affected, non-genotyped individuals, our primary comparative analysis was made with family members diagnosed after 2004—in this prospective analysis, a significant survival advantage was recorded in patients who had undergone surveillance (figure). Furthermore, clear survival benefits

Panel 2: Research in context

Systematic review

We searched PubMed with key terms including “tumor surveillance”, “early tumor detection”, “breast cancer”, “brain tumors”, “adrenocortical tumors”, “osteosarcoma”, “soft tissue sarcoma”, “leukemia”, “lymphoma”, “colon cancer”, “Beckwith-Wiedemann syndrome”, “von Hippel Lindau disease”, “hereditary breast-ovarian cancer syndrome”, and “hereditary non-polyposis coli”. We searched reference lists in articles describing surveillance protocols and predictive genetic testing in Li-Fraumeni syndrome and other cancer susceptibility disorders, as well as the published National Comprehensive Cancer Network guidelines for surveillance of specific tumours associated with Li-Fraumeni syndrome. One study³⁸ examined the use of ¹⁸F-fluorodeoxyglucose PET and CT imaging for the detection of asymptomatic cancers in *TP53* mutation carriers, and another case report documents the detection of an asymptomatic adrenocortical carcinoma with abdominal ultrasound.⁴⁰ None of the previous studies used a comprehensive approach to surveillance that examined both feasibility and effect on survival.

Interpretation

Our study shows the feasibility of a comprehensive surveillance protocol for early detection of tumours in patients with Li-Fraumeni syndrome, and its potential effect on survival. These findings can be used by clinicians to incorporate genetic screening of at-risk patients and families into clinical care, including early genetic screening in children. This information, in the context of a multidisciplinary health-care approach, can be used to enrol patients into a structured, comprehensive surveillance programme. However, multicentre prospective studies to assess the long-term outcomes of patients undergoing surveillance and investigate risk-stratification strategies to tailor guidelines and develop targeted surveillance are still needed.

were noted in screened members of family six, who had germline mutations and histological tumours identical to those of their non-screened relatives (webappendix p 2). Despite such limitations, the results of this analysis are robust to alternative statistical analyses, and will enable future multicentre studies that incorporate a larger group of patients, address cost-effectiveness considerations, and eliminate some of the inherent limitations of the present design.

Identification of the relative usefulness of different detection modalities is difficult because distinct cancers have been detected by different approaches. Additionally, a longer follow-up could reveal the detection of malignancies by specific modalities that did not identify tumours during the course of the study. The heterogeneity of tumour types and the variability of age at onset in patients with Li-Fraumeni syndrome necessitate the

implementation of a comprehensive surveillance strategy. However, other studies suggest important roles for genetic modifiers in *TP53* mutation carriers.^{41–45} As the effect of these genetic modifiers and other risk stratification characteristics become more clear, and as larger scale studies are completed in the future, specific cancer risks could be refined, which will permit focused patient-specific modifications of the surveillance approach.

Our study shows the feasibility of using non-invasive biochemical and imaging modalities in a structured, comprehensive surveillance programme to detect asymptomatic cancers among germline *TP53* mutation carriers in families with Li-Fraumeni syndrome, and indicates a potential survival advantage with this approach. Our findings lend support to the use of genetic screening in at-risk patients and families, including early genetic testing in children. Multicentre collaboration and implementation of surveillance guidelines is necessary to assess the long-term outcomes of patients. Continuous research into risk stratification strategies will help to tailor guidelines and offer more targeted surveillance to susceptible individuals.

Contributors

AV, UT, and DM participated in the design of the study, the collection, analysis, and interpretation of data, and drafting and critical revision of the paper. JS, AS, and JF participated in the collection, analysis, and interpretation of data, and critical revision of the paper. HD and AN participated in the collection of data and critical revision of the paper. JB participated in the statistical analysis and interpretation of data.

Conflicts of interest

We declare that we have no conflicts of interest.

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