ORIGINAL INVESTIGATION

Baseline Surveillance in Li-Fraumeni Syndrome using whole body magnetic resonance imaging: A Meta-Analysis

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KEY POINTS

Question
Does baseline whole body MRI detect asymptomatic cancers at a curable stage in germline TP53 mutation carriers?

Findings
Using a meta-analysis of 13 cohorts including 578 participants, the overall detection rate for previously unrecognized new localized malignancies by a single baseline WBMRI in TP53 mutation carriers was 7% (95% confidence intervals 5-9%). The false positive rate was 43%. All screen-detected new cancers were treated with curative intent.

Meaning
Baseline evaluation with whole body MRI offers important clinical utility in management of cancer risk in TP53 mutation carriers.
ABSTRACT

Importance

There are limited guidelines for clinical management in Li-Fraumeni syndrome, a multi-organ cancer predisposition condition. Whole body magnetic resonance imaging may play a role in surveillance of this high risk population.

Objective

To assess the clinical utility of whole body magnetic resonance imaging in germline TP53 mutation carriers at baseline.

Data Sources

Clinical and research surveillance cohorts were identified through the Li-Fraumeni Exploration Research Consortium.

Study selection

Cohorts that incorporated whole body magnetic resonance imaging for individuals with germline TP53 mutations were included.

Data extraction and synthesis

Data was extracted by investigators from each cohort independently and synthesized by two investigators. Random effects meta-analysis methods were used to estimate proportions.

Main outcomes and measures

The proportion of participants at baseline in whom a lesion was detected that required follow up and in whom a new primary malignancy was detected.

Results

A total 578 participants from 13 cohorts were included in the analysis. Two hundred twenty-five lesions requiring clinical follow up were detected by whole body magnetic resonance imaging in 173 participants. Sixty-one lesions were diagnosed in
54 individuals as either benign or malignant neoplasms. Overall, 42 cancers were identified in 39 individuals, with 35 new localized cancers treated with curative intent. The overall detection rate for new localized primary cancers was 7% (95% Confidence Interval 5-9%).

Conclusions and relevance

These data suggest clinical utility in baseline whole body magnetic resonance imaging in TP53 germline mutation carriers, and may form an integral part of baseline clinical risk management in this high-risk population.
Li-Fraumeni syndrome (LFS) was first described in 1969 as a highly penetrant cancer-prone syndrome.\textsuperscript{1} Formal diagnostic criteria for LFS have subsequently been developed, based on a family or personal history of a broad spectrum of early onset cancers, including sarcoma, breast cancer, adrenocortical carcinoma and brain tumors, often with more than one cancer per affected individual.\textsuperscript{2-5} Lifetime cancer risks are reported to approach 100\% for both sexes in cases identified by family history.\textsuperscript{6-8} The exceedingly high cancer risk in LFS often confers a high psychological and medical burden.\textsuperscript{9} Pathogenic variants in the tumor suppressor gene, \textit{TP53}, were first identified and subsequently found to cause about 70\% of classic LFS in 1990.\textsuperscript{10,11,12,13} Identification of germline \textit{TP53} mutation carriers has increased with increased sequencing of both germline and somatic DNA using gene panels, whole exome, and whole genome testing, due, in part, to the influence of precision medicine initiatives.

Although the clinical characteristics and molecular basis for LFS have been known for decades, no universally accepted approach exists for risk management. Current guidelines focus on breast cancer risk primarily because organ-specific surveillance measures,\textsuperscript{14-16} such as breast magnetic resonance imaging (MRI), are already widely used for screening in cognate high risk syndromes. However, because breast cancer constitutes only a proportion of the surgically resectable cancers to which \textit{TP53} mutation carriers are prone, there is a need for novel effective methods for cancer surveillance across a broad range of body or corporal sites. Recently, emerging studies suggest improved clinical outcomes for \textit{TP53} mutation carriers with intensive screening. The Toronto protocol, which incorporates whole body MRI (WBMRI) amongst other modalities, was associated with improved survival.\textsuperscript{17} Neonatal
screening for the Brazilian TP53 founder mutation resulted in adrenocortical tumours being detected at an early, more curable stage. Notably, a recent UK study detected malignancies in 14% of TP53 mutation carriers at baseline WBMRI. Psychological benefit has also been reported from participation in a LFS surveillance program.

However, in part because of the rarity of LFS, definitive evidence for the benefits of screening remain lacking.

To generate evidence for the efficacy of WBMRI as a surveillance tool for carriers of pathogenic germline TP53 mutations, we report here a meta-analysis of 13 prospective cohorts conducted in six countries. We assessed the detection rates of asymptomatic cancers using WBMRI as part of baseline assessment of TP53 mutation carriers, measured by the rate of identification of investigable lesions and new primary cancers that can be treated with curative intent.
METHODS

Study Selection

Clinical and research surveillance cohorts were identified through the Li-Fraumeni Exploration Research Consortium. Cohorts formed over the past 15 years that performed WBMRI in individuals at any age were considered (Table 1 in the Supplement). All research cohorts had ethical approval and written consent was obtained from participants or guardians as appropriate. There was no requirement for subjects to be newly diagnosed for participation in any of the studies included in this meta-analysis. All cohorts included brain in the WBMRI scan with the exception of the Huntsman Cancer Institute. All participants were asymptomatic at the time of the baseline scan. The details of imaging protocols for contributing cohorts, including the use of contrast and organ-specific sequences, are given in Tables 3-14 in the Supplement. All participants were known carriers of pathogenic TP53 mutations or were obligate carriers by pedigree.

Data Extraction and Classification

Data was extracted by investigators from each cohort and synthesised by two investigators (MB and DT). Lesions were considered investigable if further clinical follow up was required in the opinion of the study investigator, including additional imaging or biopsy. The true positive rate for WBMRI was defined as the rate of detection of localized, primary cancers that were treated with curative intent. False positive lesions were defined as considered initially neoplastic (All neoplasms in Figure 1), but which subsequently were determined on further investigation to be either benign tumors, recurrences of previous cancers, or incurable metastatic cancers.
Low grade gliomas were classified as malignant. The treatment intent (curative or palliative) following diagnosis was recorded in each case.

**Statistical Analysis**

Random-effects meta-analysis methods\(^{22}\) for proportions were used to aggregate the data from the 13 participating cohorts. Meta-analyses were performed to estimate the proportion of participants found to have one or more investigable lesions, the proportion of participants found to have one or more new primary cancers, and the proportion of investigable lesions determined to be new primary cancers, with approximate 95% confidence intervals\(^ {23}\). The between-cohort heterogeneity \( r^2 \), along with associated p-value, was estimated using the DerSimonian-Laird method. A logit transformation was used to calculate the overall proportions. Cohort participants were additionally subdivided by sex and by age group (0-17, 18-40, or >40 years of age) to identify age-dependent trends in cancer detection rates and to be consistent with prior management recommendations\(^ {17}\). Tests of subgroup differences were conducted using Cochran's Q test. All analyses were performed with R version 3.3.1,\(^ {24}\) using version 4.6-0\(^ {25}\) of the *meta* package.
RESULTS

Research Surveillance Study characteristics

This meta-analysis included 578 participants (376 female) with deleterious germline TP53 mutations from 13 cohorts who underwent baseline WBMRI between January 1, 2004 and October 1, 2016, (Table 1 in the Supplement). Of these, 134 (77 female) were 0-17 years of age, 246 (164 female) were 18-40 and 198 (135 female) were >40 years of age. Germline TP53 variant data available for participants showed 183 unique events, including 91 missense, 26 nonsense, 8 frameshift and 20 intronic variants. There were a further 38 insertions or deletions. Almost half of the participants (280/578, of whom 211 were female) had been diagnosed with at least one prior malignancy. Of the 264 female participants older than 17 years for whom information was available, 17 (6%) had a single mastectomy, and 110 (42%) had a double mastectomy.

A flowchart outlining the disposition of participants included in the meta-analysis is given in Figure 1. Of the 578 participants, 225 lesions requiring further investigation were observed in 173 participants. 42 malignant lesions were diagnosed in 39 individuals, with the majority of diagnoses based on biopsy. Four of the 42 malignant lesions were brain tumors diagnosed on imaging alone. Of the new malignancies, 35 localized primary cancers were diagnosed in 34 individuals, all of whom were treated with curative intent. The false positive rate, defined here as the proportion of suspected neoplasms that turned out to be either benign, recurrences of pre-existing cancers, or newly diagnosed metastatic cancers, was 26/61 (43%).

Meta-Analysis results
Figure 1 in the Supplement presents the meta-analysis for the proportion of participants found to have one or more investigable lesions by WBMRI. Overall, 31% (95% confidence interval (CI) 26-35%) of participants were determined to have one or more investigable lesions. No gender differences were detected (p=0.9, Cochran’s Q). The proportion of investigable lesions identified tended to increase with age (29%, 30%, 34% for those less than 18, 18-40 and >40 years of age respectively), but this increase was not statistically significant (p=0.6 overall, Cochran’s Q).

Figure 2 in the Supplement presents the meta-analysis of the proportion of individuals in whom one or more new cancers was diagnosed. Overall, 7% (95% CI 5-9%) of participants were determined to have one or more new primary malignancies. There was no significant difference between males and females (p=0.4, Cochran’s Q). The proportion of cancers identified increased with age in males (10%, 10%, 15% respectively in 0-17, 18-40, >40); females experienced a mid-life reduction in malignancies detected by WBMRI (15%, 8%, 10%), but neither trend was statistically significant (p=0.3 for females, p=0.6 for males, Cochran’s Q). A meta-analysis of the proportion of investigable lesions subsequently identified as a new primary cancer is given in Figure 3 in the Supplement. Overall, 18% (95% CI 12-27%) of investigable lesions identified by WBMRI were determined to be new primary cancers, with no gender difference (p=0.5, Cochran’s Q). The proportion of cancers identified was highest in 0-17 year olds (31%, 16%, 18% respectively in 0-17, 18-40, >40 year old participants), but this trend was not statistically significant (p=0.15 overall, Cochran’s Q).

Clinical spectrum of new primary cancers detected by WBMRI
The 35 new primary cancers identified by baseline WBMRI occurred in 34 participants (one 45 year old female with a synchronous localised chromophobe renal cell carcinoma and a localised uterine leiomyosarcoma). No new primary cancers were clinically metastatic at diagnosis. The patterns of cancers observed vary by age and gender (Table 1). All seven bone sarcomas were observed in participants under 40 years of age, with no gender difference, while five of seven soft-tissue sarcomas arose in participants over the age of 40 years. A single adrenocortical tumor was found in a child, as was a choroid plexus carcinoma. The diversity of cancers to which TP53 mutation carriers are prone was evident. Other cancers identified included carcinomas of the lung (4 participants, all over 40 years of age), kidney (17 year old female, 24 year old female and a 45 year old female), thyroid (two females 17 and 40 year of age), prostate (two males 41 and 46 years of age), and bowel (21 year old male). We only observed two breast cancers (a ductal carcinoma in situ in a 49 year old female, and an invasive ductal carcinoma in a female, 66 years of age). This may reflect the high rate of mastectomies and/or prior breast cancer diagnoses in the female population undergoing screening, as well as the use of dedicated breast MRI sequences outside WBMRI.

Brain malignancies represent an important feature of LFS. Twelve of 13 cohorts included the brain as a routine part of the WBMRI protocol. In this meta-analysis, brain tumors appeared more common in children and young adults. Of 6 brain tumors identified by WBMRI, 5 were observed in children, and one in a 33 year old woman (Table 1). We attempted to determine the ability of the dedicated brain component of WBMRI in identifying brain tumors. We compared the outcomes of WBMRI with the dedicated brain MRI where such comparisons were available (Table 2 in the
Supplement). Of 10 brain tumors identified in individuals undergoing both WBMRI as well as a dedicated brain MRI, only 5 were identified by the WBMRI while the remainder were all identified on dedicated brain MRI but not the WBMRI. Of the 5 brain tumors that were missed on WBMRI, none of the scans utilised contrast.

**DISCUSSION**

This meta-analysis provides the first statistically robust estimate of the potential clinical utility of WBMRI in screening TP53 mutation carriers. Overall, one in 14 participants undergoing their first WBMRI were found to have a primary malignancy, which was then treated with curative intent. The rate of detection of localized malignancies was remarkably consistent between individual cohorts, which were conducted across 6 countries and 13 institutions. The rate at which cancers are identified appears highest in children, and lowest in young adults, and rises again in older adults. The spectrum of cancers clearly shifts with age, with a greater number of brain tumors and bone sarcomas in children, and a range of epithelial malignancies in older adults. All screen-detected cancers were treated with curative intent, although the follow up of those participants in whom cancers were identified and treated curatively is too short to assess long term outcomes. WBMRI does not reliably identify brain tumours in TP53 mutation carriers. Another important outcome of WBMRI is the detection of benign but clinically significant lesions that are medically actionable, for example by causing organ damage through local growth or undergoing malignant transformation in this high risk population.

The absence of breast cancers in this screened population was notable. Breast cancer is the most common diagnosis amongst women with TP53 mutations under the age of
40 years but only two were identified in this meta-analysis (both over 40 years of age). This may reflect the high percentage of women who had undergone either unilateral or bilateral mastectomy prior to study entry (48%), inability of WBMRI to detect small breast lesions, or perhaps the routine use of dedicated breast MRI in women at high risk of breast cancer.

To put the results of this meta-analysis of WBMRI in TP53 mutation carriers into the context of current clinical genetics practice, we compared these results to those achieved through screening using dedicated breast MRI in women at high risk of breast cancer due to germline BRCA1/2 mutations. Breast MRI is widely approved, recommended and reimbursed for early detection of cancer in women at high risk of breast cancer. The Ontario Breast Screening Program screened 2,207 women at high risk of breast cancer using either mammography or breast MRI. The detection rate from breast MRI was 1% in this series, consistent with previous large-scale studies. The rate of screen-detected cancers in other series was similar. However, specific incidence rates for TP53 mutation carriers can be as high as 4.4%, and are often detected with pre-malignant comedo DCIS histology.

An important aspect of population screening is the false positive rate, since the investigation of lesions that subsequently turn out to be clinically insignificant is a source of potential psychological distress, medical morbidity, and cost. Almost one in three participants in this WBMRI meta-analysis were found to have an investigable lesion, and nearly one in five lesions (18%) turned out to be both malignant and appropriately treated with curative intent. Again, comparison with breast MRI is useful. The false positive rate for the combination of breast MRI with mammography
is variably reported as between 4-30%,\textsuperscript{27-29} lower than that observed in our series (43%). Importantly, a recent report on the acceptability of WBMRI in the LFS population observed that screening reduces anxiety for subjects and may provide psychological benefit.\textsuperscript{20}

There are important limitations and unanswered questions arising from this study. There was heterogeneity amongst the surveillance protocols utilised in each cohort. Subgroup meta-analyses such as these can be challenging to interpret, as the meta-analysis estimates are calculated incorporating estimated weights for each cohort rather than by simply pooling data across studies. Weighting is a critically valuable part of meta-analyses, as it reduces the influence of cohorts with small amounts of data while still including them in the aggregated analysis. Incorporation of study weights calculated independently in each subgroup or combined analysis may lead to situations such as our observation that cancer diagnosis rates in the aggregate of 18-40 year old participants is lower for males and females combined than for either alone.

Other important questions include the optimal use of WBMRI in relation to participant age and gender, since the nature and incidence of cancers varies substantially in TP53 mutation carriers. The notable excess of females to males in our study may be due to the greater engagement of females in health care.\textsuperscript{31} Additionally, it is unclear when WBMRI or other components of a surveillance program ought to be introduced as part of follow up for patients with an existing cancer diagnosis. Most cohorts contributing to this study did not use contrast, however the question of the importance of contrast as an effective component of a WBMRI protocol remains open. Careful follow up will be required to fully document any safety issues.
associated with WBMRI screening. There is much scope for optimization of WBMRI protocols with faster acquisition sequences and improved imaging technologies. Within this meta-analysis, individual cohorts varied widely in eligibility criteria for time since curative treatment for a previous cancer, although only 7 malignancies detected by WBMRI were recurrences of previous malignancies. Finally, it is not possible to estimate the false negative rate for WBMRI from our data, since this meta-analysis describes the results of a single, baseline scan. Only follow up will determine whether occult cancers were missed by WBMRI. Longitudinal follow up of TP53 mutation carriers is very limited as there has been only one study reported to date\textsuperscript{17}. Longer-term follow-up of these patients will be essential to reveal the rate of cancer development in these cohorts, identify the optimal scheduling of WBMRI, and show whether early detection of cancers in TP53 mutation carriers will translate into decreased morbidity and better survival. Estimates of the cost-effectiveness of WBMRI also lie beyond the scope of the current study, but will be important to implementation in clinical practice.

**CONCLUSION**

Cancer screening in germline TP53 mutation carriers is especially challenging because of the wide spectrum of associated malignancies. Baseline WBMRI identified a new and treatable malignancy in up to 7% of TP53 mutation carriers, confirming that this modality enables clinically useful early detection of cancer in this highly cancer-prone population across a broad range of health systems. The meta-analysis presented here suggest that WBMRI adds significantly to the armamentarium available to clinicians seeking to improve the likelihood of early tumor detection and
subsequent improved outcomes. Although further research will be required, our
findings suggest that WBMRI may be a useful component of the routine baseline
assessment of TP53 mutation carriers, in children and adults.

ARTICLE INFORMATION

Author contributions

Dr Savage, Dr Best, Dr Ballinger and Professor Thomas had full access to all data and
take responsibility for data integrity and analysis. Savage and Thomas conceived the
study. Ballinger, Khincha, Loud, Mai, Peters, Achatz, Chjiniak, da Costa, Santiago,
Eeles, Evans, Weitzel, Slavin, Nehoray, Schiffman, Naumer, Kohlman, Malkin,
Villani, Garber, O’Neill, Rednam, Bleiker, Sonke, Ruijs, Loo, Strong, Bojadzieva,
Robson, Walsh, Manelli, Stoffel and Koepppe were involved in data acquisition and/or
extraction. Ballinger and Thomas synthesized the data. Best performed the statistical
analyses. Ballinger, Best, Thomas and Savage drafted the manuscript and all authors
provided input and critical analysis.

Conflict of Interest Disclosures

The authors have no conflict of interest or disclosures to report.

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Role of the Funder/Sponsor

The funder had no role in design and conduct of the study; collection, management,  
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manuscript; and decision to submit the manuscript for publication.

Previous Presentations

This data has not been presented previously.

Additional Contributions

We thank all study participants and referring clinicians for their valuable  
contributions.

REFERENCES


FIGURE LEGENDS

Figure 1. Flowchart of disposition of participants. *Investigable were defined as those which required any intervention (e.g., further imaging, or biopsy). ¶Neoplasms were identified following biopsy in all but four cases of glioma or astrocytoma, where the diagnosis was established on imaging alone. §The total number of individuals in whom a benign or malignant neoplasm was identified includes two individuals in whom two cancers were diagnosed, including one localized primary cancer, and one recurrent cancer; and one individual in whom two new primary cancers were diagnosed.
Table 1. New localised primary malignancies detected by WBMRI

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Gender</th>
<th>Morphology and Topography (age at diagnosis, yrs)</th>
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<td>Renal and liver epithelioid angiomyolipomas (24)</td>
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*Currently under surveillance with short interval MRI, with the intent to resect at a later stage