ORIGINAL RESEARCH

Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY)

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ABSTRACT

Background Germline TP53 gene pathogenic variants (pv) cause a very high lifetime risk of developing cancer, almost 100% for women and 75% for men. In the UK, annual MRI breast screening is recommended for female TP53 pv carriers. The SIGNIFY study (Magnetic Resonance Imaging screening in Li Fraumeni syndrome: An exploratory whole body MRI) study reported outcomes of whole-body MRI (WB-MRI) in a cohort of 44 TP53 pv carriers and 44 matched population controls. The results supported the use of a baseline WB-MRI screen in all adult TP53 pv carriers. Here we report the acceptability of WB-MRI screening and effects on psychosocial functioning and health-related quality of life in the short and medium terms.

Methods Psychosocial and other assessments were carried out at study enrolment, immediately before MRI, and after MRI results, and at 12, 26 and 52 weeks’ follow-up.

Results WB-MRI was found to be acceptable with high levels of satisfaction and low levels of psychological morbidity throughout. Although their mean levels of cancer worry were not high, carriers had significantly more cancer worry at most time-points than controls. They also reported significantly more clinically significant intrusive and avoidant thoughts about cancer than controls at all time-points. There were no clinically significant adverse psychosocial outcomes in either carriers with a history of cancer or in those requiring further investigations.

Conclusion WB-MRI screening can be implemented in TP53 pv carriers without adverse psychosocial outcomes in the short and medium terms. A previous cancer diagnosis may predict a better psychosocial outcome. Some carriers seriously underestimate their risk of cancer. Carriers of pv should have access to a clinician to help them develop adaptive strategies to cope with cancer-related concerns and respond to clinically significant depression and/or anxiety.

INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare, dominantly inherited, highly penetrant cancer predisposition syndrome. The majority of families have a germline pathogenic variant (pv) in the TP53 gene.1−4 The cancers associated with LFS include breast cancer, sarcoma, adrenocortical carcinoma and brain tumours.3 4 Cancers are typically early onset (two to three decades before the median general population incidence) and there is also an increased risk of other cancers.5−7 The lifetime risk of cancer is very high for pv carriers when detected in a clinical context: almost 100% for women and 75% for men.8 However, our understanding of penetrance and cancer patterns is incomplete, as evidence from genome-wide studies has identified pv in TP53 in individuals who do not meet the LFS testing criteria.9

In 2016, the American Association for Cancer Research held a meeting of international LFS experts to develop consensus cancer surveillance recommendations. A combination of physical exams, blood tests and imaging based on the earlier ‘Toronto protocol’ was proposed.9 10 In the UK, current screening guidelines for TP53 mutation carriers recommend annual MRI breast screening in women aged 20–49 and advise considering continuing this regimen past the age of 50.11 12 Discussion of risk-reducing mastectomy is also recommended. Screening across UK genetics centres is variable, most offering a rapid review of symptoms in carriers.12

Internationally, there is increasing interest in the use of whole-body MRI (WB-MRI) as a screening tool,9−18 because, unlike other imaging approaches, ionising radiation, which may further increase cancer risk, is not used. In the UK, the SIGNIFY (Magnetic Resonance Imaging screening in Li Fraumeni syndrome: An exploratory whole body MRI) study recently reported the outcomes of WB-MRI in a cohort of 44 TP53 pv carriers and 44 matched population controls.9−17 The results supported the use of a baseline WB-MRI screen as a minimum in all TP53 pv carriers in addition to the established breast screening programme.12 Further evidence supporting the use of a baseline WB-MRI screen for early detection of
treatable tumours comes from a meta-analysis of 13 cohorts with a total of 578 TP53 pv carriers. An annual WB-MRI screen for all TP53 pv carriers is being considered for adoption as a national guideline in the UK.

Alongside clinical outcomes, it is important to evaluate possible psychosocial morbidity associated with screening. The psychosocial impact of screening with WB-MRI in TP53 carriers is largely unknown. An Australian group evaluated the use of WB-MRI in a cohort of 17 TP53 carriers. They found that participants were not overburdened and they experienced mainly positive psychological outcomes from participation. However, this study reports only preliminary results from a small cohort and larger longitudinal studies are required.

A German group evaluated the psychosocial impact of WB-MRI in a healthy general population cohort. They found that participants underestimated the personal benefit of undergoing WB-MRI and experienced no long-term effects on health-related quality of life (HRQoL) or depressive symptoms. However, those requiring further investigations for incidental findings experienced moderate or severe psychological distress.

The UK MARIBS study (study of magnetic resonance imaging (MRI) for breast screening) evaluated annual breast MRI and mammography screening in BRCA1/2 pv carriers at a significantly high risk for breast cancer. Both imaging techniques were acceptable; psychological morbidity was low, and women were significantly less anxious and depressed after screening than they had been at baseline. However, MRI caused greater distress than mammograms, and this MRI-related distress was found to persist at 6 weeks' follow-up. The psychosocial impact of annual WB-MRI in TP53 carriers requires further investigation.

We here report the short-term and medium-term psychosocial effects, HRQoL and acceptability of WB-MRI scanning carried out as part of the SIGNIFY study.

**METHODS**

**Study subjects and procedures**

The SIGNIFY study compared the incidence of malignancies diagnosed in asymptomatic TP53 pv carriers using WB-MRI screening with that in general population controls. It also assessed the incidence of non-malignant disease, the investigations required to determine the relevance of non-malignant disease, and the psychosocial impact and acceptability of WB-MRI screening. Full details of design, methods and results have been reported previously.

Participants were recruited between November 2012 and July 2016 and consisted of two cohorts: TP53 pv carriers, and age-matched (±5 years) and sex-matched population controls.

TP53 pv carriers were identified and recruited consecutively through clinical genetics services in the UK and Ireland and referred to either the Royal Marsden NHS Foundation Trust (RMH) or the Central Manchester University Hospitals NHS Foundation Trust. Inclusion criteria were carriers of a germ-line TP53 pv (not known to be low penetrance or a variant of unknown significance in the opinion of a geneticist) and aged between 18 and 60 years. Carriers with a malignancy diagnosed in the previous 5 years (except for non-melanomatous skin cancer or cervical carcinoma in situ) were excluded. Population controls were recruited in London through local advertisements and seen at the RMH. Inclusion criteria for controls were no personal history of cancer, no current symptoms suggestive of cancer and a minimal family history of cancer (no first-degree relative diagnosed <50 years, and at most only one first-degree, second-degree or third-degree relative diagnosed at any age).

All participants were invited to take part in this concurrent psychosocial study. The psychosocial impact was assessed using a set of standardised questionnaires adapted from those used in the MARIBS study. The questionnaires measured anxiety and depression, cancer worry, physical and psychological health, perceived risk of cancer, satisfaction with the process of screening, and the presence of intrusive thoughts relating to MRI screening and cancer anxiety. Those participants with a previous cancer diagnosis but meeting the eligibility criteria were asked to answer in respect to their cancer worries relating to a future diagnosis.

Questionnaire booklets were administered at seven time-points: (1) study enrolment (baseline), (2) on arrival at the MRI appointment, (3) pre-MRI and (4) post-MRI results, and (5) 12, (6) 26 and (7) 52 weeks post results. Questionnaires 1–4 were administered for all patients entered into the study. Questionnaires 5–7 were administered only for patients not diagnosed with cancer during the course of the study, as a result of the WB-MRI. Those diagnosed with cancer during the course of the study were invited to complete the questionnaires, as appropriate, up to the time of diagnosis. Each questionnaire booklet took a maximum of 20 min to complete.

**Study measures**

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale with two subscales of seven items measuring the presence and severity of anxiety and depression. Scores >11 suggest clinically significant anxiety or depression. The Cancer Worry Scale Revised is an eight-item scale that measures worry about the risk of developing cancer. A higher score indicates greater worry.

The Impact of Events Scale (IES) is a 15-item scale measuring the frequency of intrusive and avoidant thoughts about a specific life event. Respondents completed one scale for cancer and another for MRI. A higher score indicates higher distress levels; a score of >8.5 on either scale indicates clinically significant levels of distress.

The Spielberger State Anxiety Inventory-B (brief form) is a six-item scale abbreviated from the original 20-item scale and evaluates situational factors that may influence anxiety levels. In this study it was used to measure state anxiety related to the MRI scan. The Health Questionnaire (HQ) is a seven-item scale which was developed for use in a study investigating distress caused by attending routine breast screening. Respondents indicate for each stress-sensitive behaviour whether, in the last week, it has been ‘better than normal’ (score 0), same as normal (score 1) or worse than normal (score 2).

The Short Form-36 Health Survey V2.0 (SF36-II) is a 36-item generic measure of HRQoL and a seven-item scale which is converted linearly to a 0–100 scale, with a higher score representing better functioning. Summary scores are calculated for physical health and mental health.

In Perceived Risk, participants rate their perceived risk of developing cancer compared with the average person’s risk and express their lifetime risk of developing cancer as a percentage.

The Screening Satisfaction Questionnaire (SSQ) is a series of Likert scales originally designed to assess the satisfaction of individuals undergoing breast mammography and later adapted for MRI screening. The higher the score, the lower the satisfaction.

In the Acceptability of Screening, participants were asked ‘If you were offered an MRI scan next year, would you attend?’ and ‘would you encourage a family member to attend for an MRI screening scan?’
Sample size and statistical analysis
SIGNIFY had 88 participants: 44 TP53 pv carriers and 44 healthy population controls. This sample size was based on the expected cancer detection rates using WB-MRI screening in the two groups.12

If <75% of the items on any questionnaire were completed, the data were excluded. Where >75% of items were completed, a pro rata total score was calculated. The only exception was for the SF36-II, where data were excluded when <50% of the items of a subscale were completed, as recommended by the questionnaire developers.17

Descriptive statistics were calculated to summarise the characteristics of participants and the questionnaire data. Between-group differences at the various time-points were analysed using the Mann-Whitney U test, Fisher’s exact probability test and the $\chi^2$ test as appropriate; within-group changes over time were evaluated using the Wilcoxon signed-rank test and the McNemar test.

The effects of other variables such as previous cancer diagnosis and undergoing additional investigations post-MRI were analysed using the Mann-Whitney U test and the $\chi^2$ test. Alpha was set at 0.05 (two-tailed).

Data were analysed using SPSS V.24.0.

RESULTS
Sample characteristics and response rate
As previously reported, 6 of 44 (14%) carriers were diagnosed with cancer during their involvement in the study.12

All 88 (100%) participants completed the baseline questionnaires. Overall, over 52 weeks, questionnaire compliance was 85.3% (510 of 598 questionnaires administered). No significant difference in questionnaire response rate was observed between carriers and controls ($p=0.38$). Non-response was not associated with an adverse or clinically significant baseline score on a psychological scale (HADS, $p=0.28$; IES, $p=0.12$) or with a previous cancer diagnosis ($p=0.65$).

The sociodemographic characteristics of participants are shown in table 1. There were 27 women and 17 men in each cohort. The mean ages of carriers and controls were 37.6 years and 38.3 years, respectively. Most participants were white (95% carriers, 91% controls), in professional or managerial positions (50% carriers, 82% controls), and married (63% carriers, 66% controls). The number of people in professional jobs was higher in controls ($\chi^2=0.36, p=0.02$), and the control group had more people with degrees and postgraduate qualifications ($\chi^2=0.43, p=0.005$).

Hospital Anxiety and Depression Scale
The prevalence of clinically significant anxiety and depression (score ≥10) did not differ significantly between the groups at any time-point. Similarly, the mean scores of carriers and controls were similar throughout the study. At 12 weeks post-results, carriers reported more borderline and clinically significantly anxious combined (score ≥8) than controls ($p=0.036$). The anxiety scores of carriers declined significantly from baseline to preresults ($Z=-2.07, p=0.04$; table 2).

In carriers, the prevalence of clinically significant or borderline anxiety and depression in those with a history of cancer did not differ at any time-point from those without such a history (table 3). Similarly, these two groups did not differ for anxiety and depression scores (table 3).

The prevalence of clinically significant or borderline anxiety and depression did not differ significantly at any time-point for carriers requiring further investigations compared with those who did not (table 4).

Cancer Worry Scale Revised
Carriers had significantly greater mean cancer worry scores than controls at baseline ($U=499, \leq p=0.0005$), at 26 weeks’ follow-up ($U=289, \leq p=0.0005$) and at 52 weeks’ follow-up ($U=219, \leq p=0.0005$). No significant changes over time were observed in carriers. In contrast, the mean cancer worry scores declined significantly in controls between baseline and 52 weeks’ follow-up ($Z=-2.06, p=0.04$) (table 2).

Having a previous cancer diagnosis and having further investigations did not have a significant effect, at any time-point, in carriers.

IES: thoughts about cancer
Intrusive thoughts about cancer
Compared with controls, carriers had more frequent intrusive thoughts at every time-point (preresults $U=264, \leq p=0.0005$; 12 weeks’ follow-up $U=263, \leq p=0.0005$; 26 weeks’ follow-up $U=198, \leq p=0.0005$; and 52 weeks’ follow-up $U=192$, 

| Table 1 | Sociodemographic characteristics of cohorts |
|---------|---------------------------------------------|
|          | Carriers (n=44) | Controls (n=44) |
| Sex      | χ²=0.00, p=1.00 |
| Female   | 27 (61%)        | 27 (61%)        |
| Male     | 17 (39%)        | 17 (39%)        |
| Age      | t=−0.33, p=0.75 |
| Mean     | 37.6            | 38.3            |
| Range    | 19–58           | 22–59           |
| Ethnicity| χ²=1.38, p=0.71 |
| White    | 42 (95%)        | 40 (91%)        |
| Asian/Asian British | 1 (2%) | 2 (5%) |
| Chinese/Other | 0 | 1 (2%) |
| Mixed    | 1 (2%)          | 1 (2%)          |
| Education| χ²=21.39, p=<0.005* |
| None     | 2 (5%)          | 0               |
| School to 16 | 9 (20%) | 3 (7%) |
| School to 18 | 9 (20%) | 1 (2%) |
| Technical| 10 (23%)        | 5 (11%)         |
| Degree/postgraduate | 14 (32%)* | 34 (77%)* |
| Missing  | 0               | 1 (2%)          |
| Employment| χ²=2.05, p=0.56 |
| Currently employed | 36 (82%) | 38 (86%) |
| Not currently employed | 6 (14%) | 3 (7%) |
| Retired  | 2 (5%)          | 2 (5%)          |
| Missing  | 0               | 1 (2%)          |
| Marital status| χ²=0.72, p=0.70 |
| Married  | 15 (63%)        | 29 (66%)        |
| Single   | 9 (20%)         | 14 (32%)        |
| Divorced | 0               | 1 (2%)          |
| Missing  | 20              | 0               |
| Socioeconomic classification| χ²=11.22, p=0.04* |
| Professional/managerial | 21 (48%)* | 36 (82%)* |
| Skilled manual/non-manual | 15 (34%) | 5 (11%) |
| Partly skilled manual/ unskilled | 8 (18%) | 3 (7%) |
| Missing  | 0               | 0               |

*Significant difference between carriers and controls.
Table 2  Descriptive statistics and summary of psychological outcomes

| Scale                  | Study enrolment | At MRI appointment | Preresults | 12 weeks after results | 26 weeks after results | 52 weeks after results |
|------------------------|-----------------|--------------------|------------|------------------------|------------------------|------------------------|
|                        | Scale range/   | CARRIERS (n=44)    | CARRIERS (n=36) | CONTROLS (n=44) | CONTROLS (n=38) | CARRIERS (n=29) | CONTROLS (n=33) | CARRIERS (n=28) | CONTROLS (n=34) |
|                        | threshold       | (n=37)             | (n=38)                  |            |                        |                        |                        |                        |
| HADS Anxiety, mean (SD); n above threshold | 0–1             | 6.2 (3.9)*          | 4.9 (3.3)              | –          | –                      | 5.3 (3.9)*             | 4.6 (3.3)              | 5.8 (4.3)          | 4.1 (3.1)        | 5.9 (4.1)          | 4.4 (2.9)          | 5.7 (4.8)          | 4.1 (2.2)          |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
|                        | 0–7             | 28                 | 36                      | –          | –                      | 29                      | 28                      | 19                   | 34               | 22                   | 32               | 19                   | 30               |
|                        | 8–10            | 10                 | 5                       | –          | –                      | 3                       | 9                       | 5†                   | 1†               | 7†                   | 5†               | 5†                   | 2†               |
|                        | >10             | 6                  | 3                       | –          | –                      | 4                       | 1                       | 5†                   | 3†               | 2†                   | 1†               | 4†                   | 2†               |
| HADS Depression, mean (SD); n above threshold | 0–21            | 2.3 (2.5)          | 2.1 (1.9)              | –          | –                      | 2.4 (2.8)               | 2.3 (2.6)              | 2.3 (3.3)          | 1.8 (2.3)        | 2.6 (2.8)          | 2.3 (2.8)        | 3.0 (3.8)          | 2.1 (2.3)        |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
|                        | 0–7             | 42                 | 43                      | –          | –                      | 34                      | 36                      | 26                   | 37               | 27                   | 37               | 25                   | 33               |
|                        | 8–10            | 2                  | 1                       | –          | –                      | 0                       | 1                       | 1                    | 1                | 4                    | 0                | 2                    | 1                |
|                        | >10             | 0                  | 0                       | –          | –                      | 2                       | 1                       | 2                    | 0                | 0                    | 1                | 1                    | 0                |
| CWS-R, mean (SD)       | 8–32            | 14.4 (3.6)†        | 12.2 (1.7)**†          | –          | –                      | 13.6 (4.4)              | 12.1 (1.9)              | 11.0 (10.0)       | 1.7 (3.5)**†     | 11.4 (4.2)†        | 11.9 (1.8)†       | 14.5 (4.3)†        | 11.9 (1.4)**†     |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
|                        | 0–35            | –                  | –                       | –          | –                      | 11.4 (9.1)**†           | 3.0 (4.9)**†          | 8.3 (9.1)**†      | 1.8 (3.1)**†     | 11.0 (10.0)**†    | 1.7 (3.5)**†      | 9.2 (8.2)**†       | 2.1 (3.8)**†      |
|                        | 0–8             | –                  | –                       | –          | –                      | 15                      | 33                      | 18                   | 35               | 15                   | 36               | 14                   | 32               |
|                        | >8              | 21†                | 51†                     | –          | –                      | 10†                     | 31†                     | 16†                 | 21†              | 13†                 | 21†              | 13†                 | 21†              |
| IES: cancer avoidance  | 0–40            | –                  | –                       | –          | –                      | 13.3 (10.5)†           | 7.0 (8.2)**†          | 9.9 (9.0)†         | 3.8 (5.9)**†     | 13.4 (11.7)†       | 4.3 (6.7)**†       | 10.1 (9.4)**†       | 2.6 (4.6)**†     |
|                        | 0–8             | –                  | –                       | –          | –                      | 13                      | 24†                     | 12                   | 31†              | 12                   | 31†              | 12†                 | 30               |
|                        | >8              | 23†                | 141*                    | –          | –                      | 26†                     | 37†                     | 29                   | 38†              | 26†                 | 34               |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
| IES: MRI               | 0–35            | –                  | –                       | –          | –                      | 1.7 (3.6)†              | 0.5 (1.8)              | 3.1 (8.8)†         | 0.3 (1.4)†       | 1.2 (3.2)†         | 0.1 (0.3)†        | 1.0 (0.3)†         | 1.0 (0.3)†        |
|                        | 0–8             | –                  | –                       | –          | –                      | 2                      | 1                       | 26                   | 38†              | 26†                 | 34               |
|                        | >8              | 4†                 | 3†                       | –          | –                      | 24†                     | 35†                     | 29                   | 35†              | 26†                 | 31               |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
| SSAI, mean (SD)        | 6–24            | –                  | –                       | 7.2 (3.3)  | 7.3 (3.2)              | 8.1 (2.8)†             | 6.9 (2.2)†             | 7.1 (2.5)          | 7.7 (2.1)        | 7.2 (2.4)          | 7.2 (2.2)        | 7.2 (2.6)          | 7.6 (1.5)        |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
| Health Questionnaire, mean (SD) | 0–14           | 7.0 (2.6)          | 6.8 (2.2)              | –          | –                      | 8.1 (2.8)†             | 6.9 (2.2)†             | 7.1 (2.5)          | 7.7 (2.1)        | 7.2 (2.4)          | 7.2 (2.2)        | 7.2 (2.6)          | 7.6 (1.5)        |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
| SF36-II physical component summary, mean (SD) | 0–100          | 49.2 (6.1)†        | 52.1 (4.5)†            | –          | –                      | 50.7 (8.5)             | 52.0 (5.5)             | 48.4 (8.2)†        | 51.7 (9.0)†      | 47.9 (9.8)†        | 51.7 (7.3)†       | 49.3 (10.0)†        | 53.3 (8.7)†       |
|                        |                 |                    |                        |            |                        |                        |                        |                        |
| SF36-II mental component summary, mean (SD) | 0–100          | 50.2 (8.3)†        | 54.0 (6.8)†            | –          | –                      | 50.0 (10.2)            | 53.2 (9.9)             | 49.3 (10.0)        | 52.1 (9.5)†      | 49.3 (10.0)        | 53.3 (8.7)†       | 49.3 (10.0)        | 53.3 (8.7)†       |
| Risk Perception, mean (SD) | 0–100         | 68.7 (24.9)        | 27.0 (17.8)            | –          | –                      | 71.2 (24.4)            | 30.6 (16.4)            | 70.6 (25.5)        | 33.9 (18.7)       | 67.7 (27.0)        | 35.7 (19.4)       | 67.7 (27.0)        | 35.7 (19.4)       |

*Significant difference in scores between time-points (same group) compared with baseline (first) measure.
†Significant difference in scores between groups.
CWS-R, Cancer Worry Scale Revised; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; SF36-II, Short Form-36 Health Survey V.2; SSAI, Spielberger State Anxiety Inventory.
Cancer genetics

Table 3  Descriptive statistics and summary of psychological outcomes of TP53 carriers with a previous cancer diagnosis vs with those who are unaffected

| Scale                  | Study enrolment | Preresults | 12 weeks after results | 26 weeks after results | 52 weeks after results |
|------------------------|----------------|------------|------------------------|------------------------|------------------------|
|                        |                | Previous cancer (n=15) | Unaffected (n=29) | Previous cancer (n=14) | Unaffected (n=22) | Previous cancer (n=9) | Unaffected (n=20) | Previous cancer (n=12) | Unaffected (n=20) | Previous cancer (n=9) | Unaffected (n=19) |
| HADS Anxiety, mean (SD); n above threshold | 0–21 | 6.3 (3.6) | 6.1 (4.1) | 5.3 (3.8) | 5.3 (4.0) | 4.9 (4.7) | 6.3 (4.1) | 5.6 (3.8) | 6.1 (4.3) | 5.7 (3.8) | 5.7 (5.3) |
|                        | 0–7 | 10 | 19 | 11 | 18 | 6 | 13 | 8 | 14 | 7 | 12 |
|                        | 8–10 | 4 | 5 | 1 | 2 | 2 | 3 | 3 | 4 | 1 | 4 |
|                        | >10 | 1 | 5 | 2 | 2 | 1 | 4 | 1 | 4 | 1 | 3 |
| HADS Depression mean (SD); n above threshold | 0–21 | 2.1 (2.0) | 2.4 (2.8) | 2.3 (2.9) | 2.5 (2.8) | 1.7 (2.7) | 2.6 (3.6) | 2.8 (3.2) | 2.4 (2.6) | 4.1 (3.9) | 2.5 (3.8) |
|                        | 0–7 | 15 | 27 | 13 | 21 | 8 | 18 | 10 | 18 | 7 | 18 |
|                        | 8–10 | 0 | 2 | 0 | 0 | 1 | 0 | 2 | 2 | 2 | 0 |
|                        | >10 | 0 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 1 |
| CWS-R, mean (SD) | 8–32 | 14.2 (2.1) | 14.5 (4.1) | 13.1 (2.6) | 13.8 (5.1) | 13.4 (2.2) | 15.4 (4.9) | 13.0 (2.8) | 15.2 (4.7) | 14.2 (2.1) | 14.5 (4.1) |
| IES: cancer intrusion | 0–35 | – | – | 9.6 (6.7) | 12.6 (10.2)* | 8.6 (9.0) | 8.1 (9.4)* | 8.2 (8.5) | 12.6 (10.7) | 8.1 (8.4) | 9.7 (8.3) |
|                        | 0–8 | 5 | 9 | 5 | 13 | 6 | 8 | 4 | 10 |
|                        | >8 | 9 | 13 | 4 | 6 | 5 | 12 | 4 | 9 |
| IES: cancer avoidance | 0–40 | – | – | 12.5 (8.6) | 13.8 (11.7) | 9.0 (7.8) | 10.4 (9.7) | 11.5 (11.6) | 14.4 (10.0) | 7.8 (7.2) | 11.1 (10.2) |
|                        | 0–8 | 5 | 7 | 3 | 8 | 6 | 6 | 3 | 8 |
|                        | >8 | 9 | 15 | 6 | 11 | 5 | 14 | 5 | 11 |

*Significant difference in mean scores between time-points (same group).

CWS-R, Cancer Worry Scale Revised; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale.
Table 4  Descriptive statistics and summary of psychological outcomes of TP53 carriers requiring further investigations vs with those not requiring further investigations

| Scale                           | Study enrolment | 12 weeks after results* | +26 weeks after results* | 52 weeks after results* |
|---------------------------------|-----------------|-------------------------|--------------------------|-------------------------|
|                                 |                 | No investigations (n=28) | Further investigations (n=16) | No investigations (n=20) | Further investigations (n=9) | No investigations (n=18) | Further investigations (n=13) | No investigations (n=18) | Further investigations (n=10) |
| HADS Anxiety, mean (SD); n above threshold | 0–21 | 6.0 (4.4) | 5.2 (4.5) | 5.6 (3.4) | 5.6 (5.0) | 5.8 (4.8) |
|                                 | 0–7 | 18 | 14 | 13 | 13 | 6 |
|                                 | 8–10 | 5 | 3 | 4 | 3 | 2 |
|                                 | >10 | 5 | 3 | 1 | 1 | 1 |
| HADS Depression, mean (SD); n above threshold | 0–21 | 1.8 (1.9) | 1.9 (3.1) | 2.1 (2.4) | 2.7 (3.0) | 3.6 (5.1) |
|                                 | 0–7 | 28 | 18 | 16 | 16 | 9 |
|                                 | 8–10 | 0 | 1 | 2 | 2 | 0 |
|                                 | >10 | 0 | 1 | 1 | 0 | 1 |
| CWS-R, mean (SD) | 8–32 | 13.7 (2.1) | 13.2 (2.4) | 14.4 (3.6) | 14.0 (3.4) | 15.4 (5.7) |
| IES: cancer intrusion | 0–35 | – | – | 8.6 (8.4) | 10.3 (9.7) | 8.2 (6.6) |
|                                 | 0–8 | – | 11 | 9 | 9 | 5 |
|                                 | >8 | – | 8 | 9 | 7 | 8 |
| IES: cancer avoidance | 0–40 | – | – | 9.1 (7.9) | 11.0 (11.6) | 8.2 (7.6) |
|                                 | 0–8 | – | 8 | 9 | 9 | 3 |
|                                 | >8 | – | 11 | 9 | 10 | 8 |

* n=number of questionnaires returned at each time-point. Participants receiving a cancer diagnosis did not complete questionnaires beyond the time of diagnosis.

CWS-R, Cancer Worry Scale Revised; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale.
Avoidance of thoughts about cancer
Carriers reported significantly more clinically significant avoidance than controls at all time-points: at prerescuts (p=0.036), 12 weeks’ follow-up (p=0.002), 26 weeks’ follow-up (p=0.01) and 52 weeks’ follow-up (p=0.005).

Compared with controls, carriers had more frequent avoidance at every time-point (preresults U=423, p=0.005; 12 weeks’ follow-up U=304, p=0.002; 26 weeks’ follow-up U=296, p=0.005; and 52 weeks’ follow-up U=252, p=0.01).

In the control group, compared with preresults, the prevalence of clinically significant avoidance fell at 12 weeks’ follow-up (McNemar: p=0.04) and at 52 weeks’ follow-up (McNemar: p=0.01).

Avoidance scores in controls declined significantly between preresults and 12 weeks’ follow-up (Z=−2.73, p=0.006) and preresults and 52 weeks’ follow-up (Z=−3.38, p=0.001).

No significant differences in avoidance scores were found at any time-point for carriers requiring further investigations compared with those who did not.

IES: thoughts about MRI
Intrusion scores of carriers were significantly higher than those of controls at 26 weeks (U=330, p=0.05) and 52 weeks (U=284, p=0.02) postresults.

There were no significant differences in the number of participants over the threshold of clinically significant levels of intrusive thoughts about MRI between carriers and controls, or within each group, at any time-point (table 2).

Intrusion scores declined significantly in controls between preresults and 12 weeks’ follow-up (Z=−2.15, p=0.032). Scores also declined in controls between preresults and 26 weeks’ follow-up (Z=−2.68, p=0.07).

For carriers without a previous cancer diagnosis (table 3), intrusion scores fell between preresults and 12 weeks’ follow-up (12.6 vs 8.1; Z=−2.63, p=0.009).

No significant differences in intrusion scores were found at any time-point for carriers requiring further investigations compared with those who did not (table 4).

Avoidance of thoughts about MRI
There were no significant differences in clinically significant avoidance between carriers or controls, or within each group, at any time-point (table 2). The mean avoidance score of carriers was significantly higher than that of controls 26 weeks postresults (U=301, p=0.05). Mean avoidance scores did not vary significantly over time within carrier or control groups. All mean scores were very low.

Spielberger State Anxiety Inventory
No significant difference at the time of MRI was detected in state anxiety between carriers and controls and the mean scores were overall low on the scale.

Health Questionnaire
Carriers had significantly higher mean scores for stress-sensitive behaviours preresults compared with controls at 12 weeks (U=472, p=0.02) but not at other time-points. Scores did not vary significantly over time within either group.

SF36-II questionnaire
Physical function
Carriers had poorer physical functioning than controls at baseline and at 26 and 52 weeks postresults (U=645, p=0.007; U=398, p=0.02; U=318, p=0.03, respectively). However, the effect size was small and the mean values were close to the standardised mean of 50 across both groups and at all time-points.

No significant differences in mean scores were detected for physical functioning scores between baseline and any other time-point in either carriers or controls.

Mental function
Carriers had poorer mental functioning than controls at baseline (U=723, p=0.03). However, the effect size was small and the mean values were close to the standardised mean of 50 across both groups and at all time-points.

No significant differences in mean scores were detected for mental functioning scores between baseline and any other time-point in either carriers or controls.

Risk Perceptions
Carriers estimated their risk of developing cancer as higher than controls at every time-point (baseline U=183, p=<0.0005; 12 weeks U=116, p=<0.0005; 26 weeks U=165, p=<0.0005; 52 weeks U=147, p=<0.0005) (table 2).

The majority of carriers classified their risk as ‘moderately or strongly increased’ (table 5) when compared with the general population risk, with 54%–58% correctly perceiving their risk as strongly increased. Of the controls, 64%–73% perceived their risk to be ‘the same’ as the general population.

Table 5 Participants’ classification of their risk of cancer when compared with the general population risk

|             | Baseline (n=44) | 12 weeks after results (n=38) | 26 weeks after results (n=39) | 52 weeks after results (n=33) |
|-------------|----------------|-----------------------------|-----------------------------|-------------------------------|
|             | Carriers | Controls | Carriers | Controls | Carriers | Controls | Carriers | Controls |
| Lower       |          |          |          |          |          |          |          |          |
| The same    | 0        | 11 (26%) | 0        | 7 (18%)  | 0        | 10 (26%) | 0        | 6 (18%)  |
| Slightly increased | 7 (16%) | 3 (7%)   | 3 (11%)  | 2 (8%)   | 6 (19%)  | 4 (10%)  | 5 (19%)  | 5 (15%)  |
| Moderately increased | 13 (30%) | 0        | 9 (32%)  | 1 (3%)   | 6 (19%)  | 0        | 4 (15%)  | 1 (3%)   |
| Strongly increased | 24 (55%) | 0        | 15 (54%) | 0        | 18 (58%) | 0        | 15 (58%) | 0        |
Screening Satisfaction
Carriers reported higher satisfaction scores with the physical surroundings of the MRI environment than controls (U=316, p=0.03; table 6).

Acceptability of Screening
Ninety-eight per cent of carriers and 77% of controls agreed that they would attend an offered MRI scan the following year at every time-point (12, 26 and 52 weeks post-results; p=0.015).
Eighty-six per cent of carriers and 86% of controls reported that they would encourage a family member to attend for MRI screening at every time-point.

DISCUSSION
This is the first study to evaluate the psychosocial impact of WB-MRI in a cohort of TP53 pv carriers compared with a matched general population control group. Overall there were minimal adverse psychological outcomes among study participants; while carriers reported higher levels of cancer worry and depression, this was not negatively impacted by the use of WB-MRI screening.

Reassuringly, there were no statistically significant differences in the prevalence of clinically significant anxiety or depression between carriers and controls at any time-point (when using a HADS of >10). When a more stringent cut-off of 8 or more was used, the only difference between groups was at 12 weeks post-results, when carriers reported more borderline and clinically significant anxiety (34%) than controls (11%). When compared with normative data for the HADS score from a study of a large sample of general practice registrants in North West England, the prevalence of clinically significant anxiety and depression in carriers was not high. The HADS mean scores in carriers are also similar to those of other genetically high-risk populations.

Indeed, carriers with a previous cancer had lower mean scores for intrusive thoughts about cancer compared with preresults. A significant reduction in IES scores was seen at 26 weeks in controls. Scores of ≥8 (representing clinically significant levels of avoidance thoughts about cancer) also became fewer with time in controls at 12 weeks after the MRI results. The hypothesis regarding concern about MRI findings is supported by our finding of higher levels of stress-related behaviours (measured on the HQ) in carriers compared with controls immediately before the MRI results. This is further supported by the results of the MARIBS study, which reported high levels of baseline psychological morbidity that reduced post-MRI breast screening.

A small proportion of participants (cases and controls) had ongoing distress after results were provided. At 12 weeks post-results, 7% of carriers (3% of controls) had clinically significant levels of intrusive thoughts about the MRI, and 14% of carriers (8% of controls) had clinically significant levels of avoidant thoughts. There were no significant changes in the numbers of individuals affected by week 52, as numbers were small. In the general population, psychological reactions to MRI vary and a significant number of people have anxiety reactions ranging from anticipatory anxiety to a full-blown panic attack. Interventions to minimise and predict such symptoms have been documented.

Although 98% of carriers indicated that they would return for a further scan the following year, we recommend that the minority of carriers who suffer from significant MRI-related distress (be it pre-MRI, during MRI or post-MRI scan) should be offered evidence-based help in coping with future MRIs.

As expected, mean cancer-related worry scores were high in carriers and significantly higher than in controls. It is well documented that living with a TP53 pv is a psychosocial burden for patients. It is also known that living in a family with a TP53 pv has an adverse psychosocial impact regardless of_pv status. Although 98% of carriers indicated that they would return for a further scan the following year, we recommend that the minority of carriers who suffer from significant MRI-related distress (be it pre-MRI, during MRI or post-MRI scan) should be offered evidence-based help in coping with future MRIs. It could be hypothesised that carriers with a previous cancer diagnosis may have a worse psychosocial experience when undergoing cancer screening. However, a previous cancer diagnosis was not associated with any worse psychosocial outcomes. Indeed, carriers with a previous cancer had lower mean scores for anxiety at 6 and 12 months post-WB-MRI compared with unaffected carriers. This needs further exploration in a larger series, but may suggest a degree of post-traumatic growth among the participants with previous cancer diagnoses.

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Sensitive measures and interventions to manage fear of cancer recurrence are being evaluated. High levels of fear of recurrence are usually associated with psychological morbidity and poor HRQoL, as seen in carriers living at risk of multiple cancers. Therefore strategies to increase resilience and reduce cancer fear could be potentially very beneficial to improve psychosocial well-being in this group.

Importantly, no clinically significant differences were detected between carriers requiring additional investigations for an abnormality found on MRI and those requiring no additional investigations, either in the short or medium term. In McBride et al’s study, qualitative interviews found that, despite an initial high level of faith in the efficacy of WB-MRI, a large proportion of participants reported the MRI to be burdensome, particularly in

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**Table 6. Participants’ mean screening satisfaction scores**

| Convenience and access | Staff interpersonal skills | Information transfer | Physical surroundings* | Perceived technical competence | General satisfaction |
|------------------------|---------------------------|----------------------|------------------------|-------------------------------|---------------------|
| Carrier (n=37)         | Carrier (n=37)            | Carrier (n=37)       | Carrier (n=37)         | Carrier (n=37)                | Carrier (n=37)       |
| Mean (SD)              | Mean (SD)                 | Mean (SD)            | Mean (SD)              | Mean (SD)                     | Mean (SD)           |
| 7.5 (2.8)              | 6.9 (2.3)                 | 4.5 (1.5)            | 6.2 (2.3)              | 8.4 (3.0)                     | 6.2 (2.3)           |
| Possible range         | 4–20                      | 4–20                 | 4–20                   | 5–25                          | 4–20                |

*Significant difference in mean scores between groups.
those requiring additional investigations. However, this study was limited by its small numbers (nine participants were interviewed 6 months after the MRI and data collection is ongoing). We found no evidence to support this finding, with no differences reported in either HRQoL or psychosocial measures at 12, 26 or 52 weeks post initial results. It is reasonable to assume that by 12 weeks any further investigations would have been completed and participants would have known the outcome. Therefore any short-term impact on distress levels during the period of uncertainty of a diagnosis may have been missed with this study design. Overall, our data indicate that additional investigations triggered by the MRI did not add a longer-term psychosocial burden for carriers.

In terms of general HRQoL, significant differences were detected in SF36 scores between carriers and controls in both physical and mental functioning. However, this did not change over time, and all scores were similar to previously published norms. Carriers had a slightly poorer overall HRQoL, but undergoing MRI screening had no impact on HRQoL.

Only 55%–57% of carriers correctly estimated their risk of cancer at each time-point as ‘strongly’ increased when compared with the general population risk. Almost half of pv carriers underestimated their lifetime risk of cancer, 15%–20% very substantially. This may be a coping strategy rather than a shortcoming concerning information given or understood. Either way, it highlights the need for ongoing easy-to-access information and support. McBride et al found that undergoing screening and having contact with a clinician were emotionally helpful. Therefore, in addition to the utility of WB-MRI, future research should evaluate types of support for carriers undergoing screening.

The SSQ findings demonstrate very high satisfaction levels with all aspects of screening in all participants. Schmidt et al’s evaluation of WB-MRI screening in the general population found similar results. Almost all carriers (98%) stated that they would attend for a repeat scan in a year’s time, demonstrating a very high level of acceptability of WB-MRI screening. Significantly fewer controls (77%) stated they would attend for a repeat scan, perhaps because their risk of cancer was significantly lower. In both groups, 86% would recommend a relative attends a repeat scan, perhaps because their risk of cancer was significantly lower.

Therefore, in addition to the utility of WB-MRI, future research should evaluate types of support for carriers undergoing screening.

CONCLUSION

WB-MRI screening is very acceptable to carriers and is associated with minimal medium-term adverse psychosocial outcomes. The presence of a TP53 pv is well known to cause adverse psychosocial outcomes for some, but there is no evidence that WB-MRI screening exacerbated cancer worry or depression. There was evidence of a transient increase in anxiety pre-MRI, but this might have been due to anticipation of what screening might detect, rather than undergoing MRI. The study population had a high level of satisfaction with the WB-MRI screening process.

Reassuringly there was no adverse psychosocial impact observed in the carriers requiring additional investigations for an abnormality detected at MRI, and a previous cancer diagnosis may predict a better psychosocial outcome.

Some carriers seriously underestimate their risk of cancer, raising the question of maladaptive coping strategies. We recommend easy access to a clinician for all mutation carriers to help them cope with cancer-related concerns, including intrusive cancer-related thoughts and images, and to respond appropriately to clinically significant depression and/or anxiety should it occur. Any carriers who suffer from procedural anxiety related to screening should be offered help from a clinician conversant with evidence-based anxiety management techniques.
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