Original Article

Cancer Surveillance and Distress Among Adult Pathogenic *TP53* Germline Variant Carriers in Germany: A Multicenter Feasibility and Acceptance Survey

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BACKGROUND: Li-Fraumeni syndrome (LFS) is a high-risk cancer predisposition syndrome caused by pathogenic germline variants of *TP53*. Cancer surveillance has noted a significant survival advantage in individuals with LFS; however, little is known about the feasibility, acceptance, and psychosocial effects of such a program. **METHODS:** Pathogenic *TP53* germline variant carriers completed a 7-part questionnaire evaluating sociodemographics, cancer history, surveillance participation, reasons for nonadherence, worries, and distress adapted from the Cancer Worry Scale. Counselees' common concerns and suggestions were assessed in MAXQDA Analytics Pro 12. **RESULTS:** Forty-nine participants (46 females and 3 males), aged 40.0 ± 12.6 years, formed the study population; 43 (88%) had a personal cancer history (including multiple cancers in 10 [20%]). Forty-three individuals participated (88%) in surveillance during the study or formerly. Willingness to undergo surveillance was influenced by satisfaction with genetic testing and counseling ($P = .019$ [Fisher-Yates test]) but not by sociodemographics, cancer history, or distress level. Almost one-third of the participants reported logistical difficulties in implementing surveillance because of the high frequency of medical visits, scheduling difficulties, and the travel distance to their surveillance providers. Self-reported distress and perceived emotional burden for family members and partners were moderate (median for self-reported distress, 3.3; median for perceived emotional burden, 3.0). For both, the interquartile range was moderate to very high (2.7-3.7 and 3.0-3.7, respectively). **CONCLUSIONS:** Individuals with LFS require efficient counseling as well as an accessible, well-organized, interdisciplinary, standardized surveillance program to increase adherence and psychological coping. ***Cancer* 2020;126:4032-4041**.

KEYWORDS: adherence, hereditary breast cancer, Li-Fraumeni syndrome, pathogenic *TP53* germline variant, surveillance.

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Human investigations were performed after approval by an institutional ethics committee and in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from each study participant.

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INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer predisposition syndrome caused by pathogenic germline variants in the *TP53* gene and is associated with excessive lifetime cancer risks from birth onward. The cancer spectrum is broad and includes various cancer entities such as breast cancer, adrenocortical carcinoma, brain tumors, sarcomas, and leukemia.[1-3] Because radiation-induced secondary cancers have been described, surveillance methods without radiation are preferred. International guidelines currently recommend that individuals with high-risk variants of *TP53* undergo regular surveillance visits, which should include physical examinations, blood tests, abdominal sonography, colonoscopy, annual dermatologic examinations, and further imaging such as annual breast and brain magnetic resonance imaging (MRI) as well as annual whole-body magnetic resonance imaging (WB-MRI).[4-8] A recent study has noted a significant survival advantage for individuals with LFS undergoing surveillance,[4] and benefits from WB-MRI have been documented by several additional studies.[9-12] Although a structured and standardized surveillance program has not been implemented yet for routine care in Germany, specialized centers offer comprehensive surveillance according to international recommendations. Often, individuals with LFS and physicians face time-consuming, burdensome inquiries by insurance companies for coverage, and this causes another burden for the affected in addition to the cancer risks.

Little is known about the feasibility and acceptance of this extensive surveillance program for individuals with LFS. Here we investigated cancer surveillance habits and distress among adult pathogenic *TP53* germline variant carriers in Germany.

MATERIALS AND METHODS

Study Population

The study was open to adults with a class 4 or 5 *TP53* variant ("likely pathogenic" or "pathogenic") according to the American College of Medical Genetics and Genomics guidelines.[13] *TP53* germline variant carriers were recruited between December 2016 and May 2018. Most participants were identified by the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), which currently comprises 20 university hospitals and offers state-of-the-art care for women with hereditary breast and ovarian cancer (HBOC) risk variants (http://www.konsortium-familiaerer-brustkrebs.de/), including *TP53*. These individuals' *TP53* variants were identified via diagnostic multigene sequencing panels (eg, the TruRisk panel) as previously described.[14-16] In GC-HBOC centers, genetic counseling is performed by multidisciplinary teams, including a consultation with a physician/geneticist, a gynecologist, and a psychologist. The study was also open to adult individuals with LFS who were recruited by cooperating pediatric oncologists caring for families with LFS (http://www.krebs-praedisposition.de/en/).

Study Protocol

Cooperating centers identified potential participants via their respective databases and reported the number to the initiating center in Heidelberg, Germany. Participants received a study-specific questionnaire with a pseudonymized code from their center as well as a prepaid envelope. After 1 month, returned documents with the pseudonymization codes were communicated to the cooperating centers, which then recontacted their nonresponders. Candidates were included if a completed questionnaire and a signed consent form were returned. The study protocol was approved by the ethics committee in Heidelberg (S-370/2016) and by each participating center.

Study Instruments

A 7-part questionnaire with 68 items captured sociodemographic data in addition to individual and family cancer histories. This analysis included adherence to surveillance modalities, risk awareness, personal concerns, and LFS-related worries and distress (Supporting Table 1).

Adherence to Surveillance Modalities and Genetic Counseling

Adherence was assessed with 11 self-designed study-specific items (Supporting Table 1). If the participants intended to participate or had already participated in recommended surveillance measures, they were considered adherent. Participants who actively chose to perform less or stop surveillance were defined as nonadherent. If inconsistent answers regarding nonadherent or adherent surveillance were detected, participants' free-text responses were analyzed to group those individuals additionally. Counselees' retrospective experiences with genetic testing and counseling were evaluated with 5 self-designed questions (Q22-Q26 in Supporting Table 1).

Distress, Worries, and Risk Awareness

Distress and worries were assessed with the Cancer Worry Scale (5 items; Supporting Table 1).[17-21] Three

items on self-reported distress were included: burdened thoughts due to the pathogenic gene variant (Q12), impairment due to burdening thoughts (Q13), and worries about children and family members (Q16). Two items were included for the perceived emotional burden of a partner (Q14) and the family (Q15).[17-23] Average scores for distress were calculated (range, 1-5). Higher average scores indicated higher cancer worries and higher related distress. The association between adherence and distress was analyzed for each item in classes: 1) low to no distress, 2) moderate distress, and 3) quite high to a lot of perceived distress. Furthermore, Q12/Q13 and Q16 were aggregated for data analysis as well as Q14 and Q15.

Psychological and social support were evaluated with 3 self-designed questions (Q27-Q29). As described previously, we used 4 items for estimating the cancer/cancer recurrence threat and the resulting impairment in daily life (Q17-Q20).[17,18,20,24,25]

Individual Concerns and Comments

Sources of distress, individual suggestions, and comments were captured in 3 open-ended questions. To identify and describe counselees' common concerns and suggestions across the data set, we conducted a thematic analysis, which provided a systematic framework for coding qualitative data in health psychology.[26] Specifically, we applied "sources of distress" and "necessary improvements for the surveillance program" as 2 themes, whereas entire comments from participants served as the units of analysis for inductive coding and semantic categorizing. In total, we identified 37 subthemes in the open-ended section. To ensure transparency, we processed and analyzed all text-field comments in MAXQDA Analytics Pro 12.[27]

Statistical Analysis

The mainly descriptive statistical analyses were performed with Microsoft Excel, version 15.31 (170216), and SPSS 24 (SPSS Statistics V24; IBM Corporation, Somers, New York). Values are presented as means and standard deviations, medians, minima and maxima, interquartile ranges, n values, and percentages. Possible differences between groups were tested with the *t* test, chi-square test, and Fisher-Yates test. All tests were 2-sided. For correlation, we used Kendall's τ coefficient (r) and considered P values <.01 to be significant, whereas for all other tests, P values <.05 were considered statistically significant. P values were regarded as descriptive, and no correction for multiple testing was performed.

TABLE 1. Baseline Characteristics of the Study Population (n = 49)

Characteristic	Value	Characteristic	Value
Sex, No. (%)		Education, No. (%)	
Female	46 (94)	Primary school	5 (10)
Male	3 (6)	Secondary school	19 (39)
Age, median ± SD (range), y	40.0 ± 12.6 (18-66)	High school	14 (29)
Children, yes, No. (%)	30 (61)	College/university	11 (22)
Marital status, No. (%)		Country of origin, No. (%)	
Single	10 (21)	Germany	40 (82)
Single parent	2 (4)	Other	9 (18)
In a relationship	4 (8)	Smoking, No. (%)	
Married	31 (63)	Yes, currently	4 (8)
Divorced	2 (4)	No, never	32 (65)
Current occupation, No. (%)		Former smoker	13 (27)
Scholar/student	8 (16)	Psychological support, No. (%)	
Housewife	4 (8)	Yes	20 (41)
Freelancer	3 (6)	No	26 (53)
Employee	26 (53)	Not indicated	3 (6)
Pensioner	7 (14)		
Unemployed	1 (2)		
Insurance status, No. (%)		Personal cancer, No. (%)	43 (88)
State	42 (86)	Several cancer types[a]	10 (20)
Private	7 (14)	≥1 family member with cancer, No. (%)	45 (92)

[a]This includes all study participants who had at least 2 cancers.

RESULTS

Study Population

A total of 80 individuals with (likely) pathogenic *TP53* germline variants from 13 centers were contacted: 41 subjects returned the questionnaires, and 8 additional subjects contacted us directly for participation. This resulted in a final study cohort of 49 participants (46 females and 3 males). Baseline characteristics of the study population are given in Table 1. The personal cancer diagnoses are shown in Table 2. *TP53* variant details as well as family cancer histories are outlined in Supporting Tables 2 and 3. A positive familial cancer history was reported for 45 participants (92%), with a total of 88 first-degree relatives affected by at least 1 cancer diagnosis (Supporting Table 3).

Adherence to Surveillance Modalities and Genetic Counseling

Most individuals with LFS had general knowledge about recommended *TP53* germline variant–specific surveillance (n = 38 [78%]; Q6), whereas 9 (18%) were unsure, and 2 (4%) were uninformed. Surveillance modalities were followed during the study or formerly by 43 participants (88%; Q2). A total of 37 individuals (77%) remained adherent to the surveillance since their

TABLE 2. Tumor Types Among Study Participants With a Personal Cancer History (Current or Former Cancer Diagnosis) at the Time of Study Participation

Tumor Type (n = 33)	Affected Individuals, No. (%)	Multiple Tumor Types (n = 10)[a]	Affected Individuals, No. (%)
BC	27 (82)	BC + STS or melanoma or basal cell carcinoma	3 (30)
Adrenocortical carcinoma	3 (9)	BC + osteosarcoma	3 (30)
Cervical cancer	1 (3)	BC + contralateral BC + melanoma	1 (10)
Melanoma	1 (3)	BC + STS + leukemia	1 (10)
STS	1 (3)	BC + contralateral BC + CC + osteosarcoma	1 (10)
		STS + prostate cancer + stomach carcinoma	1 (10)

Abbreviations: BC, breast cancer; CC, colorectal cancer; STS, soft-tissue sarcoma.
[a]Nine females and 1 male.

LFS diagnosis, whereas 2 (4%) stopped participating in a surveillance program, and 9 (19%) intentionally attended less often than recommended; they formed the nonadherence group (n = 11 [23%]). One individual did not provide all the required information for this section and was considered a missing value. The adherence and nonadherence groups did not differ significantly in terms of the following: country of origin, health insurance or educational status, current employment, number of children, familial cancer history, psychological support, and logistical difficulties (Table 3). Logistical difficulties in implementing surveillance were stated by 13 of the 44 participants (30%); adherent participants especially claimed more organizational problems (n = 10 [77%] vs n= 3 [23%]; Table 3). Causes for declined surveillance in the nonadherence group were frequent confrontation with the condition (3 of 11) and the belief that further adherence would not be necessary after prophylactic mastectomy (2 of 11). Two female participants stopped surveillance after undergoing unilateral therapeutic mastectomy in combination with simultaneous contralateral prophylactic mastectomy for breast cancer, with one citing the frequent confrontation with cancer and the other citing organizational problems with missing cost coverage for WB-MRI. Insurance companies covered the surveillance fully for 57% (n = 28) and partially for 12% (n = 6), whereas 31% of the participants (n = 15) could not provide any information on the coverage by their health insurance.

All 6 participants without a personal cancer history showed good adherence, whereas 31 of the 43 participants with a personal cancer history did ($P = .313$ [univariate Fisher-Yates test]). Adherent individuals were more likely to be satisfied with genetic testing (32 of 37 adherent individuals vs 6 of 11 nonadherent individuals; $P = .019$ [univariate Fisher-Yates test]; Table 3) and to recommend it to family members (28 of 37 vs 4 of 11; $P = .049$ [univariate Fisher-Yates test]; Table 3).

Distress, Worries, and Risk Awareness

Many participants reported being moderately burdened by thoughts of LFS (n = 23 [47%]; top row in Fig. 1), whereas most experienced strong to very strong worries for family members (n = 28 [57%]; middle row in Fig. 1). This was also reflected in the aggregated data: average distress was moderate (median for Q12, Q13, and Q16, 3.3; interquartile range, 2.7-3.7; median for Q14 and Q15, 3.0; interquartile range, 3.0-3.7) with a moderate correlation (r) regarding these questions. Psychological support was sought significantly more often if thoughts burdened by LFS affected everyday life somewhat up to quite a lot or if everyday life was impaired by these thoughts ($P = .027$ and $P = .001$ [Fisher-Yates test]). Interfamilial communication about genetic findings was good because most participants communicated their genetic findings to their whole family (n = 36 [74%]) or parts of their family (including or not including their partner; n = 11 [22%]); 2 participants (4%) shared no information.

Thirty of the 49 individuals with LFS (61%) estimated their cancer risk adequately as quite high to very high (Fig. 2). Risk perception was not correlated with age ($r = 0.027$), educational degree ($r = 0.198$), employment status ($r = 0.141$), a familial cancer history ($r = 0.065$), or a personal cancer history ($r = 0.126$).

TP53 germline variant–related distress did not differ significantly between the adherence and nonadherence groups (Table 4).

Sources of Distress and Improvements for the Surveillance Program

Thirty-seven of the 49 participants (76%) provided free-text comments. Data-driven thematic analysis of these comments yielded 2 main factors for distress and 3 main themes for improvements in the current cancer surveillance. Extensive worries about their children's health were described. Moreover, patients had to cope with the

TABLE 3. Adherence to Surveillance Modalities Among Study Participants

	Adherence Group (n = 37), No. (%)	Nonadherence Group (n = 11), No. (%)	*P*
Children			
Yes	23 (76.7)	7 (23.3)	1.000
No	14 (77.8)	4 (22.2)	
Partnership			
Married/stable partner	9 (69.2)	4 (30.8)	.458
Other	28 (80)	7 (20)	
Country of origin			
Germany	28 (71.8)	11 (28.2)	.950
Other	9 (100)	0 (0)	
Education			
Primary school + secondary school	18 (75)	6 (25)	1.000
High school + college	19 (79.2)	5 (20.8)	
Insurance status			
Statutory	33 (80.5)	8 (19.5)	.327
Private	4 (57.1)	3 (42.9)	
Personal cancer diagnosis			
Yes	31 (73.8)	11 (26.2)	.313
No	6 (100)	0 (0)	
Familial cancer history			
Yes	34 (77.3)	10 (22.7)	.660
No	3 (75.0)	1 (25.0)	
Logistical problems			
Yes	10 (76.9)	3 (23.1)	1.000
No	24 (80)	6 (20)	
Never performed surveillance	0 (0)	1 (100)	
Psychological support			
Yes	12 (63.2)	7 (36.8)	.195
No	22 (84.6)	4 (15.4)	
Undecided	3 (100)	0 (0)	
I would reperform genetic testing			
Yes	32 (84.2)	6 (15.8)	.019[a]
No	0 (0)	2 (100)	
Undecided	5 (62.5)	3 (37.5)	
I would recommend genetic testing to family members			
Yes	28 (87.5)	4 (12.5)	.049[a]
No	1 (50)	1 (50)	
Undecided	8 (57.1)	6 (42.9)	

Only variables with a difference greater than 15% between the adherence and nonadherence groups were considered and are listed. One individual did not provide all information in this questionnaire section and was considered a missing value. The chi-square test or the Fisher-Yates test was used for all *P* values in this table. 4 particpants did not answer this question: adherent group n = 3; nonadherent group n = 1).
[a]$P < .05$.

significant burden tied to the frequent follow-up visits and the effort related to the difficult process of scheduling appointments at cancer care centers frequently located far from their homes. With respect to potential improvements in current practice in Germany, participants strongly pleaded for a standardized surveillance protocol and a central point of contact for the various diagnostic procedures. One participant expressed her belief in the benefit of surveillance as follows: "At the time of my cancer diagnosis, I was 22 years old. I would like to live a long life and participate in regular, comprehensive, and unified surveillance modalities." In addition, participants articulated an urgent need for further information on their condition, including cancer prevention strategies and updates on new therapeutic options. Finally, participants requested that health insurance companies cover surveillance modalities fully and directly without the need to file multiple claims and objections. Specifically, patients demanded that health insurance companies cover the costs for WB-MRI.

DISCUSSION

This is the first study within Germany to evaluate adherence to cancer surveillance recommendations, surveillance-related distress, and psychological aspects in individuals with LFS. In a previous publication, Lammens et al[28] investigated recommended surveillance modalities in the Netherlands, related adherence, and its psychological impact. After studying *TP53* variant carriers (n = 27) and family members at 50% risk for LFS (n = 18) who had not received genetic testing, they postulated that the majority of individuals

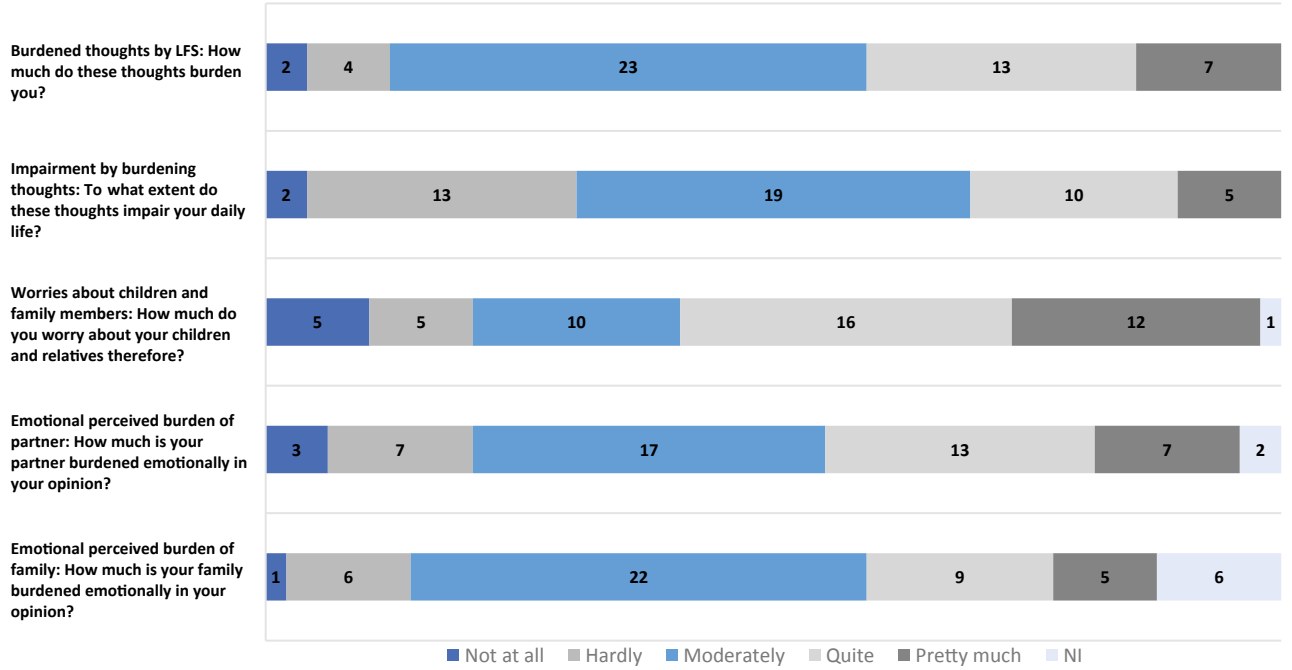

FIGURE 1. Hereditary cancer–related distress in pathogenic *TP53* germline mutation carriers. The questions refer to cancer-related thoughts within the week before study participation (Q12-Q16 in Supporting Table 1) in analogy to our previous work and the work of others (Vetter et al,[17] Keller et al,[19] Eismann et al,[20] Schott et al,[21] Codori et al,[24] and Vernon et al[25]). Absolute numbers are indicated. LFS indicates Li-Fraumeni syndrome; NI, not indicated.

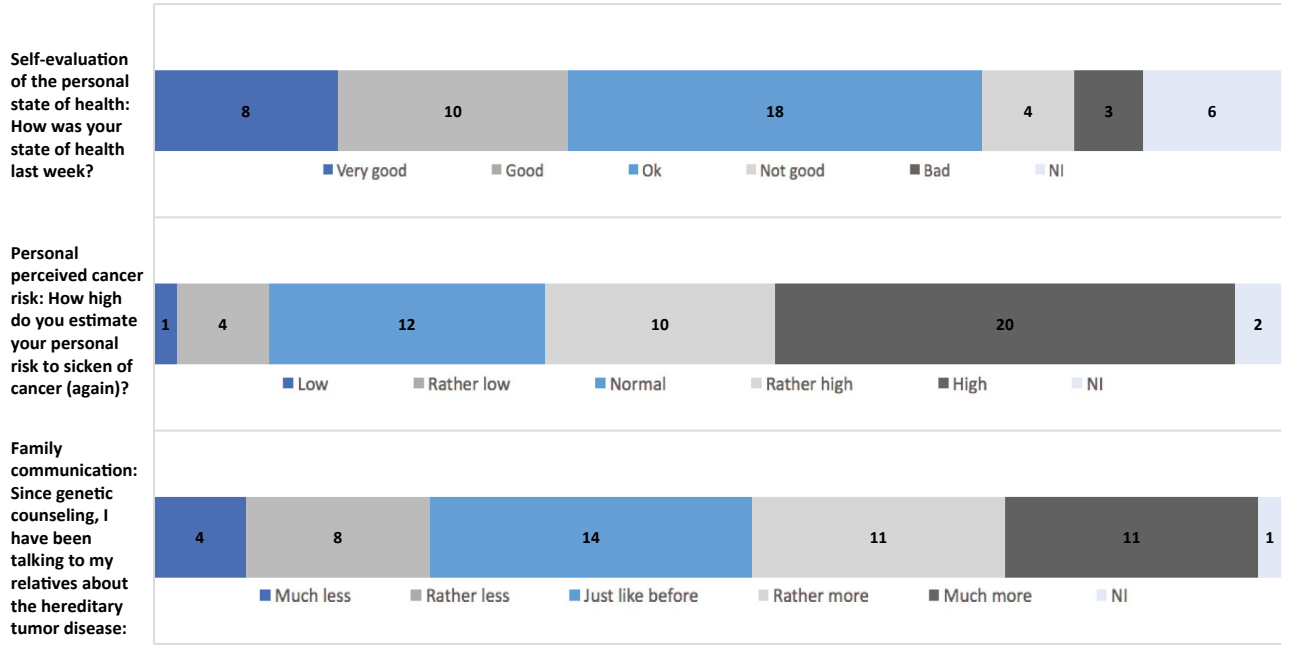

FIGURE 2. Self-evaluation of the personal state of health, cancer occurrence risk, and communication in the family after diagnosis in *TP53* germline mutation carriers (Q17, Q18, and Q29 in Supporting Table 1) in accordance with our previous work and the work of others (Vetter et al,[17] Keller et al,[18] Eismann et al,[20] Codori et al,[24] and Vernon et al[25]). Absolute numbers are indicated. NI indicates not indicated.

TABLE 4. Relationship Between Adherence, Nonadherence, and LFS-Related Distress and Sensitivity to Risk

	Adherence Group (n = 37), No. (%)	Nonadherence Group (n = 11), No. (%)	*P*
Burdened thoughts by LFS			
Not at all to hardly	5 (100)	0 (0)	
Moderate	19 (82.6)	4 (17.4)	.275
A lot to quite a lot	13 (65)	7 (35)	
Worries about children and family members			
Not at all to hardly	8 (80)	2 (20)	
Moderate	5 (55.6)	4 (44.4)	.176
Strong to quite strong	24 (85.7)	4 (14.3)	
Perceived emotional burden of partner			
Not at all to hardly	7 (100)	0 (0)	
Moderate	17 (77.3)	5 (22.7)	.504
A lot to quite a lot	11 (78.6)	3 (21.4)	
Perceived emotional burden of family			
Not at all to hardly	6 (60)	4 (40)	
Moderate	13 (76.5)	4 (23.5)	.371
A lot to quite a lot	16 (84.2)	3 (15.8)	
Perceived personal cancer risk			
Low to rather low	2 (50)	2 (50)	
Normal	11 (91.7)	1 (8.3)	.147
Rather high to high	22 (73.3)	8 (26.7)	

Abbreviation: LFS, Li-Fraumeni syndrome.
The respective questions are shown in Supporting Table 1 (questions Q12, Q14-Q16, and Q18). Only variables with a difference greater than 15% between the adherence and nonadherence groups were considered and are listed. The Fisher-Yates test was used for all *P* values in this table. The questioned were grouped upon topic, If one answer of the grouped questions was missing, mean of the remaining grouped questions is shown. If more than one question of the group was not answered tehe value was set missing.

with LFS believed in the benefits of cancer surveillance, which provided a feeling of security and control, and this increased adherence. Disbelief in the utility of surveillance and avoidance behavior due to fear or too much organizational effort were reasons for nonadherence. Interestingly, our adherent cohort reported more organizational problems, and this supported their essential motivation regarding surveillance.

The notion that WB-MRI may reduce mean anxiety and distress and has no adverse psychological outcomes has been also confirmed by other investigators.[10,29,30] It has rather been suggested that psychological distress could be reduced by WB-MRI and surveillance.[10,28,30]

A recent case-control study by Bancroft et al[29] analyzed the effects of WB-MRI on psychological functioning and quality of life in adult *TP53* variant carriers in comparison with healthy population controls over time. Even though *TP53* variant carriers had significantly more cancer worries than controls, WB-MRI did not negatively influence their psychological well-being and quality of life independently of previous personal cancer diagnoses. Bancroft et al described the highest values for anxiety at the baseline, however, without the detection of any MRI-specific anxiety. The decreased distress over time after the availability of results supported the hypothesis about concerns regarding MRI findings.

Interestingly, follow-up examinations due to MRI abnormalities revealed no significant difference in psychological malfunctioning,[29] although other studies have argued that a high false-positive rate for malignant lesions by WB-MRI could be associated with psychological distress.[10,29]

In contrast, a previous systematic review of psychological burden and quality of life with respect to both high cancer risk and intensified surveillance revealed increased distress among individuals with hereditary cancer syndromes at high risk for developing multiple tumors and a lower quality of life (especially females and individuals with a personal or familial cancer history).[31] This study by Gopie et al[31] argued for screening tools to identify distressed individuals, and this should be considered in future studies with individuals with cancer predisposition syndrome to further address the impact of their personal experiences as well as coping methods. As for further coping strategies among individuals with LFS, family structures as well as familial collective support and responsibility were detected as having an outstanding role that should be considered in the future.[32]

Notably, one-quarter of individuals with LFS did not follow current surveillance guidelines. A previously described reason for nonparticipation in surveillance programs among individuals with LFS is missing insurance coverage.[4] In Germany, an individual cost coverage request is normally submitted before the initiation of surveillance. Currently, cost coverage often requires time-consuming, burdensome explanations. An obligation for insurance companies to cover cancer surveillance for individuals with LFS does not yet exist in

Germany. In addition to coverage issues, logistical difficulties in implementing surveillance may lead to nonadherence. The required methods challenge specialists in interdisciplinary centers including hemato-oncology, gastroenterology, gyneco-oncology, dermatology, and radiology departments. The frequent appointments, requiring self-initiation and often scheduled at tertiary care centers far from the patients' homes, cause a burden that could potentially be prevented through, for example, the introduction of modern technologies such as cell phone applications that monitor and summarize surveillance appointments, updates, and recommendations. Standard interventions such as blood tests and coloscopies could be performed by local centers, whereas other measures requiring more LFS-specific expertise (eg, WB-MRI) could be offered by specialized cancer predisposition centers conducting translational research.

Surprisingly, our study did not identify logistical problems and insurance status as factors significantly influencing adherence. Instead, satisfaction with interdisciplinary counseling significantly improved adherence in our cohort, and this supports the necessity of a well-structured counseling process before and after genetic testing. The fact that 2 participants stopped surveillance after mastectomy indicates that there is still a need for more information and support to handle the potential LFS cancer spectrum, and this needs to be addressed in counseling. Bakhuizen et al[33] discussed how especially those women who do not have a typical LFS family history but experience an early onset of breast cancer need appropriate counselling strategies, and this needs to be examined in larger studies.

Interestingly, the observed moderate individual distress and cancer worry levels were lower than expected in light of the literature and the high lifetime cancer risk (up to 100%) for those with LFS.[1,30,31,34-38] A considerable proportion of the study participants (31%) underestimated their own cancer risk, and this was consistent with previous reports by others.[29,37] This factor could have been caused by insufficient information, repression of thoughts on the disease, or a lack of knowledge about *TP53* germline variant–associated cancer risks in both patients and their physicians. Familial cancer experiences with death and traumatic grief can cause high psychological distress and insecurity and influence cancer risk perception.[24,38-42] In particular, a high number of cancer diagnoses among first-degree relatives in families with LFS and being a healthy variant carrier caused greater cancer-specific distress among individuals with LFS.[38] Our probands were mostly recruited on the basis of the GC-HBOC criteria, which also include women with early-onset breast cancer and without the classic LFS cancer spectrum or family history. Therefore, a direct comparison with previous studies is problematic. Nevertheless, our results confirm the notion that worries about family members and children are severe. Self-reported distress about relatives was identified by nearly 60% of the participants and was expressed in open comments describing extensive worries, particularly about children's health. This is in accordance with findings by Inhestern et al,[43] who reported that 1 of 3 cancer survivors were strongly concerned about the impact of their disease on their children. Although having children and, in particular, having younger daughters were found to be significant predictors for good adherence in individuals with HBOC in our previous investigations,[17] the current study did not identify this association except for distress. Another study detected that *TP53* germline variant carriers were concerned about the burden to which they were exposing their partner in case of early death, including caring for surviving children.[44]

Our study was limited by a self-selection bias of participating *TP53* germline variant carriers. Active study decliners or nonresponders could avoid confrontation with their genetic disease, and this possibly correlated with decreased adherence to surveillance and a higher level of distress. In contrast, study participants could be more cooperative and most likely had a better coping attitude toward follow-up, surveillance, and distress. Furthermore, most participants were recruited via the GC-HBOC and were preselected by their HBOC family history. Therefore, a specific study population with a potentially milder LFS phenotype was addressed. This study and its statistical analyses are limited by the small sample size and differing time points for cancer, genetic testing, and surveillance, although this cohort for this rare syndrome is, to our knowledge, the first to be addressed within Germany.

Despite these limitations, our results support the need for and acceptance of a well-structured, interdisciplinary program for adult *TP53* germline variant carriers. Our results did not show excess distress, and adherence was acceptable. Carriers of a pathogenic germline variant in *TP53* suffer from increased fears about themselves and their family members. Our results support the need for optimization of the current surveillance system in Germany for individuals with LFS to facilitate adherence. Counseling influences adherent behavior; therefore, a clearly structured plan is desirable not only for individuals with LFS but also for health care providers to get the most recent information about this rare disease. Ongoing

studies are aimed at developing "individual-risk-adapted" surveillance programs and studying the associated psychosocial burden and needs as well as further translational aspects of LFS.

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AUTHOR CONTRIBUTIONS

Nathalie Rippinger: Coordination of exchange with cooperating centers, collection of data, writing and editing of the manuscript, statistical analyses, and approval of the final article. **Christine Fischer:** Main statistical work and approval of the final article. **Markus W. Haun:** Writing of the section about *TP53* germline mutation carriers' individual concerns, editing of the manuscript, and approval of the final article. **Kerstin Rhiem:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Sabine Grill:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Marion Kiechle:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Friedrich W. Cremer:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Karin Kast:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Huu P. Nguyen:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Nina Ditsch:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Christian P. Kratz:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Julia Vogel:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Dorothee Speiser:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Simone Hettmer:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Hanno Glimm:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Stefan Fröhling:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Dirk Jäger:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Stephan Seitz:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Andrea Hahne:** Patient recruitment, approval of the final article. Imad Maatouk: Review of the study questionnaire (on the basis of previous publications), and approval of the final article. **Christian Sutter:** Revision of genetic reports, revision of the manuscript, and approval of the final article. **Rita K. Schmutzler:** Patient recruitment through centers, editing of the manuscript, and approval of the final article. **Nicola Dikow:** Revision of genetic reports, revision of the manuscript, design of the study questionnaire (on the basis of previous publications), and approval of the final article. **Sarah Schott:** Design, development, and initiation of the study, supervision of data analysis and data interpretation, writing and editing of the manuscript (as senior responsible author), project development, design of the study questionnaire (on the basis of previous publications), and approval of the final article.

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