Cancer surveillance for patients with Li-Fraumeni Syndrome in Brazil: A cost-effectiveness analysis

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Summary

Background In Brazil, there is a higher prevalence of Li-Fraumeni Syndrome (LFS) compared to worldwide, due to the founder mutation in the *TP53* gene p.R337H. However, a large portion of the population, that depends on National Health Care System, does not have access to effective screening through the Toronto Protocol guidelines that enables early diagnosis and improves overall survival. Population strategies for early cancer detection recommended in Brazil are limited and additional screening is not offered to patients at a high risk, leading to late diagnoses and higher cancer mortality. This study aims to assess the cost-effectiveness of introducing annual screening that follows the Toronto Protocol for patients diagnosed with LFS in Brazil.

Methods A Markov decision analytic model was developed to estimate cost-effectiveness of 1,000 LFS carriers under surveillance and non-surveillance strategies over a patient's lifetime. The main outcome was the incremental cost-effectiveness ratio (ICER), expressed as cost per additional life year gained, comparing surveillance and non-surveillance strategies in p.R337H *TP53* carriers.

Findings For females, the model showed a mean cost of $2,222 and $14,640 and yielded 22 and 26·2 life years for non-surveillance and surveillance strategies, respectively. The ICER for early cancer surveillance versus no surveillance was $2,982 per additional life year gained. For males, the model predicts mean lifetime costs of $1,165 and $12,883 and average life years of 23·5 and 26·3 for non-surveillance and surveillance strategies, respectively. This amounts to an ICER of $ 4,185 per additional life year. Surveillance had 64% and 45% probabilities of being the most cost-effective strategy for early cancer detection in female and male carriers, respectively.

Interpretation The adoption of surveillance for patients diagnosed with LFS by the Brazilian National Health Care System is cost-beneficial for both males and females.

Resumo

Introdução No Brasil, há uma maior prevalência da Síndrome de Li-Fraumeni (LFS) em comparação ao mundo, devido à mutação fundadora no gene *TP53* p.R337H. No entanto, uma grande parte da população brasileira, que depende do Sistema Único de Saúde (SUS), não tem acesso a um rastreamento eficaz através das diretrizes do Protocolo de Toronto, que possibilitam o diagnóstico precoce e ganho em sobrevida dos portadores da síndrome. As estratégias populacionais para detecção precoce do câncer recomendadas no Brasil são limitadas e o rastreamento adicional não é oferecido a pacientes de alto risco, levando a diagnósticos tardios e maior mortalidade por câncer. Este estudo tem como objetivo avaliar a relação custo-efetividade do rastreamento anual, conforme o Protocolo de Toronto, para pacientes diagnosticados com LFS no Brasil.

Métodos Foi desenvolvido o modelo analítico de decisão Markov para estimar a relação de custo-efetividade de 1.000 portadores da LFS sob estratégias de vigilância e de não-vigilância durante a vida útil do portador. O principal

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[1] The majority of work was completed while at the University of North Carolina, NC, USA.

desfecho é a razão de custo-efetividade incremental (ICER), que expressa qual o custo adicional por ano de vida ganho, comparando as estratégias de vigilância e não-vigilância em portadores da mutação p.R337H *TP53*.

Resultados Para as mulheres, o modelo demonstrou o custo médio de $2.222 e $14.640 e resultou em 22 e 26·2 anos de vida útil para as estratégias de vigilância e não-vigilância, respectivamente. O ICER para rastreamento precoce do câncer versus nenhum rastreamento foi de $2.982 por ano de vida adicional ganho. Para os homens, o modelo prevê custos médios de vida de US$ 1.165 e US$ 12.883 e anos de vida médios de 23·5 e 26·3 anos para estratégias de vigilância e não-vigilância, respectivamente. Isto equivale a um ICER de US$ 4.185 por ano de vida adicional ganho. A realização do rastreamento conforme o Protocolo de Toronto tem probabilidades de 64% e 45% de ser a estratégia mais custo-efetiva para a detecção precoce do câncer em portadores do sexo feminino e masculino, respectivamente.

Interpretação A adoção do rastreamento para pacientes diagnosticados com LFS pelo Sistema Único de Saúde Brasileiro é custo-efetiva tanto para portadores do sexo masculino quanto feminino.

Research in context

Evidence before this study

PubMed, MEDLINE and Scielo were searched for cost-effectiveness studies of Li-Fraumeni Syndrome published in English or Portuguese up to Nov 5, 2021, using the terms "Li-Fraumeni Syndrome" AND "surveillance" AND "cancer" AND "*TP53*" AND "economic modelling" OR "cost-effectiveness" OR "cost-benefit" OR "cost-utility". Our search identified one study. The cost-effectiveness article published in 2019 evaluated patients with Li-Fraumeni Syndrome who were submitted to screening using the Toronto Protocol. This study also used the Markov model for this analysis and the results showed that cancer surveillance in this population is cost-effective. The first author of this study is one of the authors of our article. To our knowledge, there is no published study that performs a cost-effectiveness analysis in carriers of the p.R337H *TP53* Brazilian variant. In Brazil, there is a higher prevalence of Li-Fraumeni Syndrome (LFS) due to the founder mutation in the *TP53* gene p.R337H, however, a large portion of the population that depends on National Health Care System, does not have access to effective screening through the Toronto Protocol guidelines that enables early diagnosis and improves overall survival.

Added value of this study

In this cost-effectiveness analysis, we developed a Markov decision analytic model to estimate the incremental cost-effectiveness ratio (ICER) compared surveillance and non-surveillance strategies in Brazilian p.R337H *TP53* carriers. This model predicts for female a ICER for early cancer surveillance of $2,982 per additional life year gained and for males a ICER of $4,185 per additional life year.

Implications of all evidence available

The adoption Toronto Protocol surveillance for LFS patients by the Brazilian National Health Care System is cost-effective for both males and females. This data, which specifically assesses the Brazilian germline variant of TP53, aims to expand access to diagnosis of Li-Fraumeni Syndrome and cancer surveillance in a population that has limited health insurance coverage, leading to high incidences and mortality from cancer. By doing an effective screening is possible to change the history of those carriers, leading to an increasing survival.

Introduction

Li-Fraumeni Syndrome (LFS) is an autosomal dominant condition that predisposes to a high risk for cancer development. Germline pathogenic variants in the *TP53* gene are the underlying cause of the syndrome. LFS is characterized by early onset tumours, including childhood cancers.[1] Premenopausal breast cancer, soft tissue sarcomas (STS) and osteosarcomas, adrenocortical carcinomas and central nervous system (CNS) tumours are the core tumour spectrum. Lymphomas, lung cancer, gastrointestinal cancer and melanoma have also been described in carriers.[2] A study conducted by the National Institutes of Health in 2016 showed that the cumulative cancer risk was 50% by age 31 years among females with *TP53* mutation and 50% by age 46 years among males, and nearly 100% by age 70 years for both

sexes.[3] The incidence of carriers in the world population is estimated to be 1 in every 5,000 to 1 in every 20,000, although further studies are needed to determine an accurate population incidence.[4,5]

In Brazil, there is a higher than the global incidence of LFS due to the presence of the founder mutation in the *TP53* gene, c.1010G>A; p.Arg337His (p.R337H), which encodes the p53 protein. This variant was initially described in children with adrenocortical carcinoma in the South and Southeast of the country. Previous studies have estimated that the p.R337H *TP53* mutation occurs at a frequency of about 1:300 individual (0·3%) in these regions, which is much higher than the estimated frequency of other germline *TP53* mutations.[6−8] Carriers of the p.R337H variant have a milder penetrance, with a cumulative lifetime cancer risk of 50 to 60%.[7] It is estimated that 15 to 20% will develop cancer before the age of 30, compared to 50% of patients with the classic form of the syndrome.[8] The tumuor spectrum is similar to other *TP53* p.R337H carriers, however, there is a higher occurrence of adrenocortical carcinomas, papillary thyroid cancer, kidney cancer and lung adenocarcinoma.[9] Breast cancer is the most frequent tumour in p.R337H female carriers, with the mean age of onset is 40 years old, while the average onset diagnosis in classical LFS occurs at 32 years old.[7,9]

Screening and management in LFS carriers following the Toronto Protocol guidelines enables early diagnosis and improves overall survival.[10,11] Annual rapid whole-body magnetic resonance imaging (WB-MRI) enables diagnosis of malignant neoplasms in up to 9% of asymptomatic carriers in a cohort of 44 germline *TP53* mutation carriers.[12] The majority of newly diagnosed cancers diagnosed at an early stage can be treated with curative intent.[12,13] Breast cancer screening in females are part of the strategies that have been shown to be effective in early detection of cancers. (*Supplementary material* 1). Although there are no studies that validate the Toronto protocol strategy for variants of moderate penetrance such as p.R337H, previous studies have shown different cohorts of LFS patients, including a large proportion of Brazilian p.R337H *TP53* carriers, evaluated with whole-body MRI (WB-MRI) screenings and the results indicated that cancer screening based on WB-MRI facilitated the early detection of malignant neoplasms and it was characterized by lower recall rates and fewer follow-up invasive investigations.[14]

It is estimated that there are approximately 300,000 *TP53* p.R337H carriers in Brazil. Despite the high prevalence of LFS, molecular tests and cancer screening for patients with LFS are available to a limited number of individuals in Brazilian population who have supplementary health insurance.[8] Genetic testing for the *TP53* gene is not available through the National Health Care System (Sistema Único de Saúde, SUS) and, thus is limited to a small share of the population able to pay for supplementary insurance or out-of-pocket testing.

Population strategies for early cancer detection recommended by SUS are limited and include annual cervical exam starting at age 25, biannual mammogram starting at age 50 for women and annual faecal occult blood test at age 50 for males and females. Because a significant portion of the population does not have access to genetic testing, additional screening may not be offered to patients at high-risk of developing cancer, potentially leading to late diagnosis in this population, with a negative impact on the survival and quality of life of these patients. In addition, cascade testing would not be offered to their family members, who are at 50% risk of being carriers, and may not be aware of how to reduce their risk of developing cancer. This study aims to evaluate the cost-effectiveness of introducing annual screening that follows the Toronto Protocol for patients diagnosed with Li-Fraumeni Syndrome in Brazil. Screening can detect tumours early, which is advantageous for the patient, who is more likely to undergo curative care and has a higher chance of survival. This study compares the cost of care and life years of 1000 hypothetical patients under the non-surveillance (current) SUS strategy and surveillance (Toronto Protocol) strategy, in order to determine the cost-effectiveness, from the perspective of SUS, of changing strategies. This is estimated separately for males and females, given the differences in costs and, especially, types of tumours, for each sex.

Methods

This analysis received ethics approval from the Hospital Sírio-Libanês Ethics Committee, waiving informed consent for the use of anonymized data (number 4.646.823).

To estimate the costs and benefits of the surveillance and non-surveillance strategies, a Markov decision analytic model was used to simulate the lifetime of 1000 patients diagnosed with Li-Fraumeni Syndrome under both regimes.[15] The average cumulative costs and life years for each strategy produced by the model are then used to calculate an incremental cost-effectiveness ratio (ICER), which is the average additional cost per additional year of life gained under the surveillance strategy compared to no surveillance. The model was estimated separately for men and women, due to the differences in possible tumours and surveillance costs between sexes. In Brazil, there is no widespread consensus on the willingness to pay for an additional year of life saved, but commonly used thresholds are one to three times the current Gross Domestic Product (GDP) per capita. For conservative purposes, the surveillance strategy is considered cost-effective if the ICER falls below the GDP per capita.[16]

Model description

The model is structured as follows (Figure 1). Patients begin each year-long cycle at one of four possible health
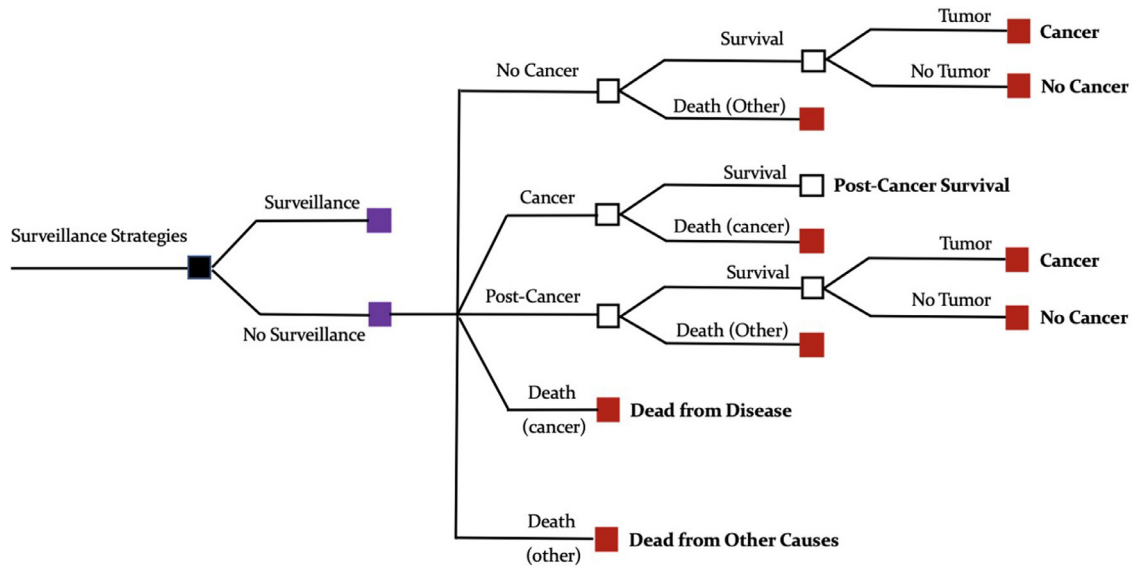
Figure 1. Structure of the Markov Decision. This diagram illustrates the structure of the Markov Decision Analytic model. At the (black) decision node, Li-Fraumeni carrier patients are assigned to either the surveillance or non-surveillance strategies, for the duration of their lifetime. The purple nodes are Markov nodes, after which the patients transition between health states and where they re-enter the model every cycle (year). The omitted flow of states after the surveillance strategy Markov node follows the structure shown after the non-surveillance strategy Markov node. Thereafter, white squares represent chance nodes, after which a probability is assigned to each event. The red nodes represent terminal nodes, which indicate in what state the patient re-enters the model in the next cycle (year).

states: 'no cancer', 'cancer', 'post-cancer survival' or 'deceased'. All patients enter the model at birth and are assumed to be free of cancer at this stage. One year later, the patient can either continue in the 'no cancer' state, transition to a 'cancer' state, or die of other causes. Those who develop cancer can either survive and begin the following cycle as a post cancer survivor or die of cancer. Post cancer survivors can either develop another primary tumour and proceed to the 'cancer' state, or not, in which case they return to the 'no cancer' state the following cycle. In each cycle patients can also die of unrelated causes. The average lifetime costs and life years are then calculated for 1000 hypothetical patients treated under the surveillance and non-surveillance branches. The model was constructed using TreeAge Pro 2017 (TreeAge Software, Williamstown, MA).

Model parameters

Patient outcomes. The age-specific probabilities of developing cancer are estimated from cancer registries according to the method developed by Fay et al.[17] This method implicitly assumes that the probabilities of developing successive cancers are independent. The data come from two large hospitals in São Paulo, Brazil, and include 380 individuals. The data record all tumours developed over each patient's lifetime (if any), the type of tumour, and the age and sex of the patient (Table 1). Observations are split according to sex and the

resulting two sex-specific datasets are bootstrapped. The rates of tumour development are estimated and converted into annual age-specific probabilities of developing cancer for each bootstrapped sample.[17] The final probabilities used in the model are averages across these samples. Due to the scope of the data, it is not possible to reliably estimate age-specific probabilities for ages above 70. The model therefore assumed the definition of a life cycle to be 70 years. Note that overall life expectancy in Brazil is roughly 75 years for men and 78 years for women; as a result, this assumption should not drastically affect cost-effectiveness results.[18]

Cancer mortality probabilities were based on the study by Villani et al.[11], which tracked LFS patients under surveillance and no surveillance and documented the patients' survival rates. Patients were assumed to be screened from birth to death under the surveillance strategy according to the Toronto protocol. Similar to the Canadian patients in Villani et al.[11], it is reasonable to assume 100% compliance with screening in this setting given that SUS provides free healthcare and patients are aware of their LFS diagnosis and increased cancer risk. Patients in the non-surveillance strategy were assumed to follow general population screening guidelines. All-cause mortality probabilities were obtained from the 2017 mortality tables published by the Brazilian Institute for Geography and Economics (IBGE).[18] Life years were discounted at a 3% annual rate.

Variable	Base Case Estimate	Standard Deviation	PSA Distribution	Source
Female Parameters				
Age-Specific Probability of Tumour Development				
Age 0 — 20	0·019	0·105	Beta	Hospital Records
Age 21 — 40	0·022	0·106	Beta	Hospital Records
Age 41 and over	0·058	0·115	Beta	Hospital Records
Cost of Surveillance				
Age 0 - 17	R$ 2,730	R$ 182	Gamma	SUS
Age 18 — 20	R$ 2,510	R$ 167	Gamma	SUS
Age 21 — 25	R$ 2,824	R$ 188	Gamma	SUS
Age 26 and over	R$ 2,905	R$ 193	Gamma	SUS
Cost of Cancer Treatment				
Early Stage	R$ 16,030	R$ 1,068	Gamma	SUS
Late Stage	R$ 18,588	R$ 1,239	Gamma	SUS
Cost of Cancer Survivorship (Surveillance)				
Age 0 — 17	R$ 6,752	R$ 450	Gamma	SUS
Age 18 -20	R$ 6,532	R$ 435	Gamma	SUS
Age 21 - 25	R$ 6,846	R$ 456	Gamma	SUS
Age 26 and over	R$ 6,297	R$ 461	Gamma	SUS
Cost of Cancer Survivorship (Non-Surveillance)				
Age 0 - 49	R$ 8,805	R$ 588	Gamma	SUS
Age 50 and over	R$ 8,829	R$ 588	Gamma	SUS
Male Parameters				
Age-Specific Probability of Tumour Development				
Age 0 - 20	0·016	0·104	Beta	Hospital Records
Age 21- 40	0·014	0·103	Beta	Hospital Records
Age 41 and over	0·024	0·106	Beta	Hospital Records
Cost of Surveillance				
Age 0 - 17	R$ 2,730	R$ 182	Gamma	SUS
Age 18 — 25	R$ 2,510	R$ 167	Gamma	SUS
Age 26 and over	R$ 2,591	R$ 172	Gamma	SUS
Cost of Cancer Treatment				
Early Stage	R$ 13,822	R$ 921	Gamma	SUS
Late Stage	R$ 14,688	R$ 979	Gamma	SUS
Cost of Cancer Survivorship (Surveillance)				
Age 0 — 17	R$ 5,908	R$ 383	Gamma	SUS
Age 18 — 25	R$ 5,688	R$ 379	Gamma	SUS
Age 26 and over	R$ 5,769	R$ 384	Gamma	SUS
Cost of Cancer Survivorship (Non-Surveillance)				
Age 0 — 49	R$ 6,903	R$ 460	Gamma	SUS
Age 50 and over	R$ 6,904	R$ 460	Gamma	SUS
Non-Sex-Specific Parameters				
Probability of Survival				
Surveillance	0·84	1·59	Beta	Villani et al
Non-Surveillance	0·49	3·28	Beta	Villani et al
Probability of Early Stage Cancer				
Surveillance	0·78	0·195	Beta	Buys et al / Jarvinen et al / Oluwole et al
Non-Surveillance	0·53	0·169	Beta	Buys et al / Jarvinen et al / Oluwole et al
Discounting				
Effectiveness	0·03	0·01	Normal	
Cost	0·03	0·01	Normal	

Table 1: Model parameters.
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Age	Female screening cost (Real/ US dollars)	Male screening cost (Real/ US dollars)
0 - 17 yo	R$ 2730 / US$ 472	R$ 2730 / US$ 472
18 - 20 yo	R$ 2511 / US$ 434	R$ 2511 / US$ 434
20 − 25 yo	R$ 2825 / US$ 488	R$ 2511 / US$ 434
25 − 75 yo	R$ 2905 / US$ 502	R$ 2591 / US$ 447

Table 2: **Annual cost of Toronto protocol per patient.**
[a]The quotation of US dollar to Brazil Real of March 29, 2021 was used (1 USD = 5.79 BRL).

Costs. The cost effectiveness analysis was carried out from the national health care system's perspective, and therefore all costs included in the model are direct medical costs resulting from surveillance or cancer treatment. Estimates were based on the national health care system's report of costs associated with each type of medical procedure, which is publicly available on their website.[19] All costs were discounted at a 3% annual discount rate.

The yearly cost of surveillance for a patient was constructed by summing the individual costs of all medical procedures necessary to satisfy the Toronto Protocol screening guidelines (Table 2). If a particular procedure is not offered by SUS, it is replaced in the study for its equivalent, i.e., a combination of brain, cervical, thoracic, upper, and lower limbs, abdominal and pelvic MRI is equivalent to a WB-MRI. Although prophylactic bilateral mastectomy is an option to reduce the risk for breast cancer in LFS carriers, we did not include its cost in screening as risk-reduction mastectomy is not offered to germline mutation carriers by the national public health system. These costs took age-specific differences into account. The cost of cancer treatment and post cancer survival were constructed in a similar way, separately for five main different types of cancer and, within those, separately for early and late-stage diagnosis. The final averages were weighted by the frequency of each type of cancer observed in the data and the probability of early versus late-stage diagnosis under surveillance

and non-surveillance strategies (Table 3). These probabilities were estimated by several different studies,[20−23] and compiled by Tak et al.[24]

Sensitivity analyses
One-way Sensitivity Analyses (OWSA) and Probabilistic Sensitivity Analysis (PSA) were conducted to lend credibility to the results given the uncertainty in parameter estimation.[25,26] One-way sensitivity analyses explore the impact that individual parameter uncertainty has on the model results; PSAs explore the impact of joint uncertainty of all parameters on the model results. The confidence interval (CI) for the age specific probability of developing cancer was calculated based on the continuity corrected Wilson's score interval.[27] The confidence intervals for other probabilities were obtained from the original studies they came from. For the PSA, we used beta distributions to model probabilities (e.g., cancer occurrence, cancer survival, general survival) and gamma distributions to model costs (e.g., surveillance, cancer treatment, post-cancer survivorship). Using the distributions generated by the PSA, we calculated 95% confidence intervals for the mean costs and effectiveness by taking the 2.5th percentile and 97.5th percentile for the lower and upper end estimates, respectively. We also generated a cost-effectiveness acceptability curve to show the percentage of PSA iterations for which each strategy was preferred.

	Early stage (Real/ US dollar[a])	Late stage (Real/ US dollar)
Adrenal cancer	R$ 3425 / US$ 591	R$ 18416 / US$ 3181
Soft tissue sarcoma	R$ 23886 / US$ 4125	R$ 12416 / US$ 2144
Brain cancer	R$ 17314 / US$ 2990	R$ 14073 / US$ 2431
Breast cancer	R$ 18872 / US$ 3259	R$ 23980 / US$ 4141
Colon cancer	R$ 33075 / US$ 5712	R$ 29504 / US$ 5096
Osteosarcoma	R$ 24426 / US$ 4219	R$ 22995 / US$ 3971
Melanoma	R$ 16299 / US$ 2815	R$ 15775 / US$ 2725
Lung cancer	R$ 18737 / US$ 3236	R$ 16016 / US$ 2766
Thyroid cancer	R$ 3367 / US$ 582	R$ 7214 / US$ 1246
Prostate cancer	R$ 14344 / US$ 2477	R$ 18454 / US$ 3187

Table 3: **Annual cost of cancer treatment.**
[a] The quotation of US dollar to Brazil Real of March 29, 2021 was used (1 USD = 5.79 BRL).

Role of the funding source

The authors received no financial support in the study design, collection, analysis, interpretation of data, writing report or decision to submit this paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Female patients

For female patients, the model predicts mean lifetime costs of R$ 12,869 (US$ 2,222; 95% CI: R$ 4,063 - R$ 27,106) and R$ 84,771 (US$ 14,640; 95% CI: R$ 56,983 - R$ 134,797) for non-surveillance and surveillance strategies and average life years of 22·0 (95% CI: 12·4, 34·3) and 26·2 (95% CI: 17·7, 40·3), respectively. This amounts to an ICER of R$ 17,267 (US$ 2,982) per additional life year, little more than half the value of the WTP threshold.

According to the one-way sensitivity analysis (OWSA), the base case results are most susceptible to the probability of survival for surveillance patients. The second most important parameter determining the results is the probability of cancer, followed by the probability of survival for non-surveillance patients (Figure 2). The OWSA that varies the probability of survival for surveillance patients is the only one that leads to an ICER confidence interval that contains the WTP

threshold. This probability would have to be less than 0·7 in reality for the surveillance strategy to stop being cost-effective at the R$30,000 WTP threshold.

Probabilistic Sensitivity Analysis yields a mean lifetime cost of R$13,630 (US$2,354) and R$88,080 (US$15,212) and average life years of 223 and 27·0 for non-surveillance and surveillance strategies, respectively. The corresponding ICER is R$15,908 (US$2,747). At the conservative WTP threshold of R$30,000, there is a 64% probability that surveillance is the most cost-effective strategy. At the more flexible threshold of R$90,000, there is an 82% probability that surveillance is the most cost-effective strategy (Figure 3).

Male patients

For male patients the model predicts mean lifetime costs of R$ 6,749 (US$1,165; 95% CI: R$ 239 - R$ 20,534) and R$ 74,596 (US$12,883; 95% CI: R$ 52,316 - R$ 123,238) and average life years of 23·5 (95% CI: 12·6, 38·8) and 26·3 (95% CI: 17·5, 43·8) for non-surveillance and surveillance strategies, respectively. This amounts to an ICER of R$ 24,236 (US$4,185) per additional life year, which is also significantly lower than the WTP threshold even though it is substantially higher than the female ICER.

According to the one-way sensitivity analysis (OWSA), the base case results are also most susceptible to the probability of survival for surveillance patients. Similar to female patients, the second most susceptible parameter is the probability of cancer, followed by the
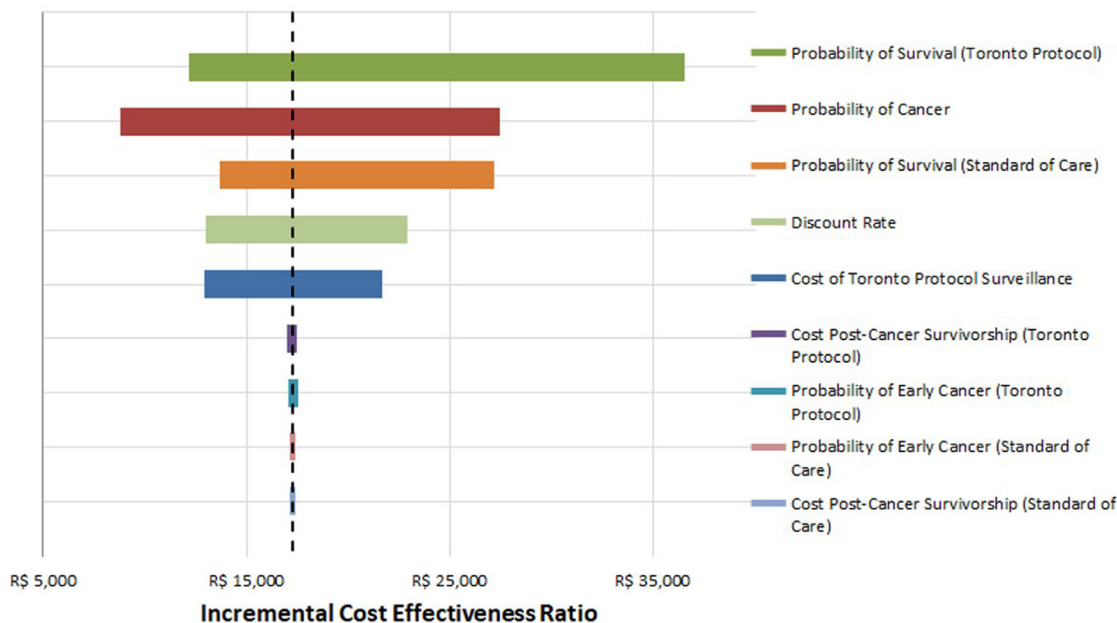

Figure 2. Tornado diagram summarising changes in the ICER of surveillance vs non-surveillance strategies for female patients. Tornado diagram summarising changes in the ICER of surveillance vs non-surveillance strategies for female patients as a result of one-way sensitivity analyses. Each horizontal bar depicts the range of ICER values achieved when the only that parameter is varied over its confidence interval. The vertical dotted line plots the base case mean ICER of R$17,267.
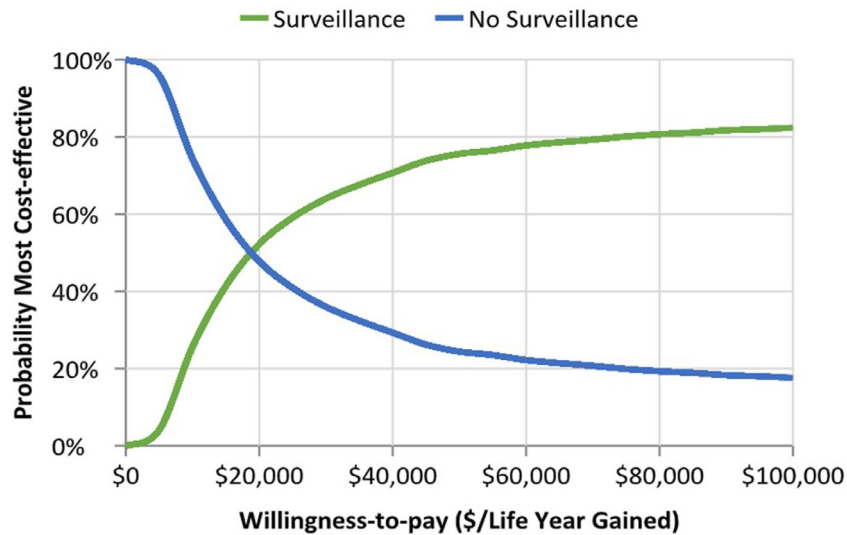
Figure 3. Cost-Effectiveness Acceptability Curve for female patients under surveillance and non-surveillance strategies. Cost-Effectiveness Acceptability Curve (CEAC) based on 1000 Monte Carlo simulations for female patients under surveillance and non-surveillance strategies. These PSA-generated curves depict the percent of iterations in which each strategy is the most cost-effective across a range of willingness to pay thresholds. At the WTP threshold of R$30,000, surveillance has a higher likelihood of being cost-effective.

probability of survival for non-surveillance patients (Figure 4). In contrast to the female OWSA, all three of these parameters, when varied, separately lead to ICER confidence intervals that contain the WTP threshold, as does the OWSA for the discount rate. The probability of cancer and the probability of survival for the surveillance strategy would have to be less than 0·014 and 0·78 in reality for the surveillance strategy to stop being cost-effective at the R$30,000 WTP threshold. If the probability of survival for non-surveillance patients was in reality above 0·56 or if the cost of the Toronto protocol exceeded approximately R$ 3,200 (US$552), this would also reverse the cost-effectiveness result of the base-case scenario. Moreover, if the discount rate considered was above 4·5%, this would also mean surveillance would not be cost-effective considering a WTP of R$ 30,000.

Probabilistic Sensitivity Analysis yields a mean lifetime cost of R$7,401 (US$1,278) and R$74,450 (US$12,858) and average life years of 24·2 and 27·4 for non-surveillance and surveillance strategies, respectively. The corresponding ICER is R$21,841 (US$3,772). At the conservative WTP threshold of R$30,000, there is a 45% probability that surveillance is the most cost-effective strategy. At the more flexible threshold of R$90,000, there is a 62% probability that surveillance is the most cost-effective strategy (Figure 5).

Discussion

This study evaluates the cost-effectiveness of the Toronto surveillance protocol for males and females diagnosed with LFS in Brazil, from the National Health Care System's perspective. Surveillance provides a survival benefit between 4·7 and 3·2 life-years for females and males, respectively, and is cost-effective according to the most conservative WTP threshold in both cases. Broadly, the results are robust to the sensitivity analyses conducted, especially if we consider the less conservative WTP threshold (equivalent to three times the Brazilian GDP per capita). Moreover, surveillance for female patients is more cost-effective (lower ICER) and results in a larger survival benefit than surveillance for male patients, which is indicative of the importance of modelling the cost-effectiveness separately by sex.

The survival benefit findings are in line with other studies that estimate the cost-effectiveness of cancer surveillance for high-risk populations. Tak et al.[24] reported that the adoption of Toronto Protocol surveillance for LFS patients in the United States results in a gain of four life-years. Jorgensen et al.[28] investigated the cost-effectiveness of screening for patients predisposed to pancreatic cancer and found that it can increase life expectancy by five to seven years. Olsen et al.[29] found that surveillance for families at risk of hereditary nonpolyposis colorectal cancer (Lynch syndrome) adds one year on average to their lifespan. On the other hand, these studies differ markedly from our study in terms of costs of surveillance and cancer treatment, due to differences in the structure of the national healthcare system between countries. This analysis finds much smaller ICERs than the ones documented by the aforementioned studies, which is
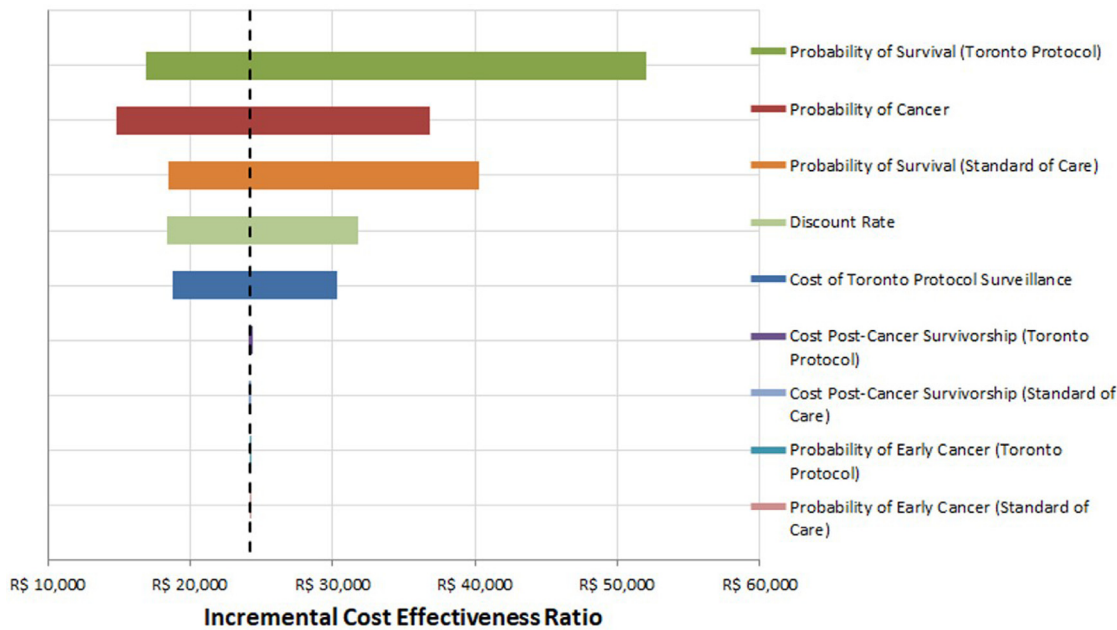
Figure 4. Tornado diagram summarizing changes in the ICER of surveillance vs non-surveillance strategies for male patients. Tornado diagram summarising changes in the ICER of surveillance vs non-surveillance strategies for male patients as a result of one-way sensitivity analyses. Each horizontal bar depicts the range of ICER values achieved (x-axis) when the model is kept constant and only that parameter is varied over its confidence interval. The vertical dotted line plots the base case mean ICER of R$24,236.
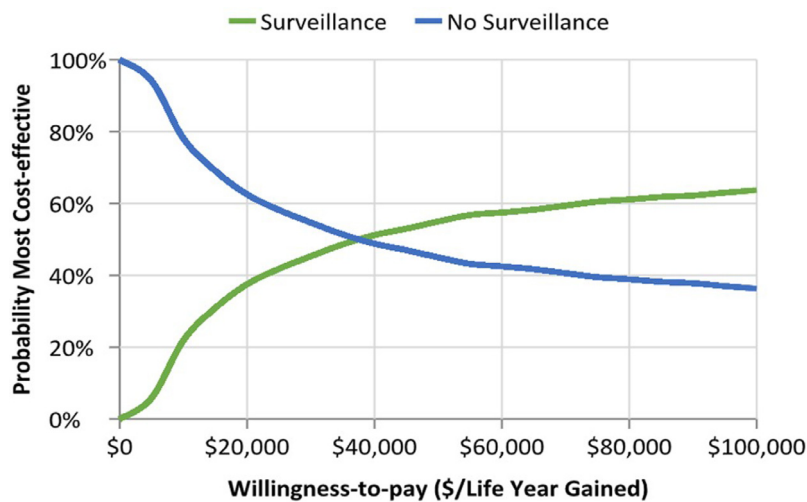

Figure 5. Cost-Effectiveness Acceptability Curve for male patients under surveillance and non-surveillance strategies. Cost-Effectiveness Acceptability Curve (CEAC) based on 1000 Monte Carlo simulations for male patients under surveillance and non-surveillance strategies. These PSA-generated curves depict the percent of iterations in which each strategy is the most cost-effective across a range of willingness to pay thresholds. At the WTP threshold of R$30,000, surveillance is the most cost-effective strategy for 45% of iterations.

also consistent with the lower WTP threshold in Brazil.

A number of strengths in the model lend credibility to our results. Firstly, the availability of the cost incurred by the government for each medical procedure offered by SUS enables the exact calculation of both the average costs of the Toronto Protocol and the average costs of cancer treatment. Secondly, the age-specific probability of cancer is estimated based on first-hand data from a large number of Brazilian families, which also permits the estimation of cost-effectiveness separately for each sex. The fact that the results are substantially different

between sexes suggests that estimating the model separately improves accuracy, and therefore reliability. Finally, the model's predicted frequency of at least one tumour by the age of 30 is similar to the published literature for individuals with LFS.

The model also has some important limitations. The probability of survival is based on one study by Villani et al.[11] which tracks 59 patients under surveillance for a median of 32 months (IQR 12-87 months) in the United States and Canada. The tumours diagnosed in LFS carriers in the Villani et al. study[11] were mainly brain tumours, soft tissue sarcomas, breast cancer, osteosarcomas and adrenocortical carcinoma. However, in our data, p.R337H *TP53* carriers developed mostly breast cancer, soft tissue sarcoma, adrenocortical carcinoma, lung cancer, thyroid cancer, prostate cancer and brain tumours. Therefore, the probabilities of survival are not exactly reflective of the Brazilian LFS population, and may be imprecisely estimated, but nonetheless provide the best approximation there is of cancer survival probabilities for LFS carriers in Brazil. Reassuringly, under the one-way sensitivity analysis that varies probability of survival, the surveillance strategy remains cost-effective for females and for males, if we consider the less conservative measure of WTP for the latter. Another limitation is that it was not feasible to add indirect patients' costs, such as travel costs, additional food expenses, or work absence. The Toronto protocol screening strategy will require the patient to be absent from work at least one day once a year, which will probably lead to extra costs.

The age-specific probabilities of developing cancer are calculated following the method in Fay et al.[17], which requires that the individual is cancer free up to each specific age. By using this method to calculate probabilities of developing successive cancers in our model, we are assuming that the probabilities of developing different instances of cancer are independent. Although this is a strong assumption and therefore a limitation of the study, this is still the most precise method to calculate age-specific probabilities of developing cancer from the prevalence of cancer. The undiscounted mean life-years for females were 42·2 and 56·5 for the non-surveillance and surveillance arms, respectively, resulting in an incremental effectiveness of 14·3 life years. The undiscounted mean life-years for males were 47·9 and 57·1 for the non-surveillance and surveillance arms, respectively, resulting in an incremental effectiveness of 9·2 life-years. With that being said, the one-way sensitivity analysis shows that varying the probability of developing cancer leads to, in the most extreme case, an ICER that is still below R$30,000 for females (Figure 2). This result supports the cost-effectiveness of the surveillance strategy and hence the main result of the paper.

Moreover, the measure of effectiveness in this study is life-years, which fails to capture important implications of both surveillance and non-surveillance strategies for quality of life. This is likely to overestimate the true ICER, for example, because earlier cancer diagnoses that result from surveillance avoid the need for more intensive and taxing treatments, such as chemotherapy, promoting a healthier life. On the other hand, the non-adjusted ICER may be underestimated because there are indirect costs associated with cancer screening, such as forfeited wages and time, which also affect quality of life. Unfortunately, there is currently not enough information available to measure effectiveness in terms of quality-adjusted life years, and therefore this remains to be addressed by future research.

Moreover, the results presented here assume that the Brazilian National Healthcare System, SUS, would be able to expand its services and offer surveillance for LFS patients. In reality, there would be a fixed cost associated with building the structure needed to offer surveillance in all clinics, or patients would have to travel to clinics that already offer it. In addition, currently, in some cases a patient has to wait for a few months to schedule a procedure. This would be particularly damaging for surveillance procedures since the timing of cancer screening is crucial to the surveillance strategy's effectiveness.

Conclusions

The results of this study suggest, nonetheless, that the adoption of Toronto Protocol surveillance for LFS patients by the National Health Care System, SUS, would be cost-beneficial for both males and females, given the WTP threshold. Future studies with more context-specific data and quality adjusted life years would provide further evidence supporting the cost-benefit of offering surveillance for patients with Li-Fraumeni Syndrome in Brazil.

Contributors

All authors have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Frankenthal, Alves and Achatz.

Acquisition, analysis, or interpretation of data: All authors.

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Administrative, technical, or material support: Achatz.

Study supervision: Achatz.

Data sharing statement

De-identified data will be available upon request to the corresponding author.

Declaration of interests

Authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100265.

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