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Cost-Effectiveness of Colorectal Cancer Surveillance in Hodgkin Lymphoma Survivors Treated with Procarbazine and/or Infradiaphragmatic Radiotherapy

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ABSTRACT

Background: Hodgkin lymphoma survivors treated with infradiaphragmatic radiotherapy (IRT) and/or procarbazine have an increased risk of developing colorectal cancer. We investigated the cost-effectiveness of colorectal cancer surveillance in Dutch Hodgkin lymphoma survivors to determine the optimal surveillance strategy for different Hodgkin lymphoma subgroups.

Methods: The Microsimulation Screening Analysis-Colon model was adjusted to reflect colorectal cancer and other-cause mortality risk in Hodgkin lymphoma survivors. Ninety colorectal cancer surveillance strategies were evaluated varying in starting and stopping age, interval, and modality [colonoscopy, fecal immunochemical test (FIT, OC-Sensor; cutoffs: 10/20/47 μg Hb/g feces), and multi-target stool DNA test (Cologuard)]. Analyses were also stratified per primary treatment (IRT and procarbazine or procarbazine without IRT). Colorectal cancer deaths averted (compared with no surveillance) and incremental cost-effectiveness ratios (ICER) were primary outcomes. The optimal surveillance strategy was identified assuming a willingness-to-pay threshold of €20,000 per life-years gained (LYG).

Results: Overall, the optimal surveillance strategy was annual FIT (47 μg) from age 45 to 70 years, which might avert 70% of colorectal cancer deaths in Hodgkin lymphoma survivors (compared with no surveillance; ICER:€18,000/LYG). The optimal surveillance strategy in Hodgkin lymphoma survivors treated with procarbazine without IRT was biennial FIT (47 μg) from age 45 to 70 years (colorectal cancer mortality averted 56%; ICER:€15,000/LYG), and when treated with IRT and procarbazine, annual FIT (47 μg) surveillance from age 40 to 70 was most cost-effective (colorectal cancer mortality averted 75%; ICER:€13,000/LYG).

Conclusions: Colorectal cancer surveillance in Hodgkin lymphoma survivors is cost-effective and should commence earlier than screening occurs in population screening programs. For all subgroups, FIT surveillance was the most cost-effective strategy.

Impact: Colorectal cancer surveillance should be implemented in Hodgkin lymphoma survivors.

Introduction

Hodgkin lymphoma survivors treated with infradiaphragmatic radiotherapy (IRT) and/or procarbazine-containing chemotherapy have a higher risk of developing colorectal cancer in comparison with the general population with a relative risk between 2 and 7 (1–6). Overtime, the treatment for Hodgkin lymphoma changed resulting in a better survival and therefore these patients have a higher chance of developing late adverse events, among which the development of second primary malignancies (7). Colorectal cancer surveillance may be indicated as a higher prevalence of (advanced) adenomas and serrated polyps has been shown (6). Colonoscopy surveillance has the possibility to remove benign precursor lesions and to detect colorectal cancer in an earlier stage. Therefore, colorectal cancer surveillance potentially could decrease colorectal cancer incidence and improve colorectal cancer related mortality in Hodgkin lymphoma survivors. However, tailored recommendations are lacking for this population.

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It is unknown whether surveillance could lead to a clinically meaningful reduction in colorectal cancer mortality for Hodgkin lymphoma survivors diagnosed at an adult age. In the United States, colonoscopy surveillance is recommended for young adults who survived childhood cancer (including Hodgkin lymphoma) diagnosed before the age of 21 years and were previously treated with IRT. However, so far patients treated with procarbazine-containing chemotherapy have not been included in the recommendations (8). Moreover, despite surveillance being recommended, participation rates in colonoscopy surveillance have been low among cancer survivors. An alternative colorectal cancer surveillance modality would be a noninvasive stool test, like a fecal immunochemical test (FIT) or multitarget stool DNA test (mt-sDNA), which were found to identify advanced neoplasia among Hodgkin lymphoma survivors diagnosed at an adult age (9). However, it is still unclear from which age to start colorectal cancer surveillance and which surveillance modality—colonoscopy or stool test—would be optimal and if it should vary according to previous Hodgkin lymphoma treatment.

In this study, we performed a cost-effectiveness analysis using a microsimulation modelling approach to determine the optimal colorectal cancer surveillance strategy for Hodgkin lymphoma survivors in the Netherlands, including both colonoscopy and stool test surveillance.

Materials and Methods

We adjusted well-established Microsimulation Screening Analysis-Colon (MISCAN-Colon; refs. 8, 10–13) model to reflect the Hodgkin lymphoma survivor population. Subsequently the model was used to evaluate benefits, harms, and costs of a range of potential surveillance strategies. An incremental cost-effectiveness analyses were performed to determine which strategy is optimal.

MISCAN-colon model

We adjusted the existing MISCAN-Colon model for the Dutch general population to reflect the colorectal cancer and the other-cause mortality risk observed among Hodgkin lymphoma survivors. MISCAN-Colon is a validated microsimulation model described extensively in previous papers (8, 10–13).

Adaptions of the MISCAN-colon model to Hodgkin lymphoma survivors

The adjustments for the Hodgkin lymphoma population were based on a large Dutch cohort study that aimed to prospectively assess the prevalence of colorectal neoplasia in Hodgkin lymphoma survivors, selecting. Five-year Hodgkin lymphoma survivors with first treatment performed between 1965 and 1995. The treatment strategies of that study were in accordance with treatment protocols of the European Organisation for Research and Treatment of Cancer. However, treatments for recurrence were not standardized. The adjustments are described in **Table 1**. In our analysis, we adjusted an existing version of the MISCAN-Colon model to reflect colorectal cancer risk and life expectancy of Hodgkin lymphoma survivors (**Table 1**). We adjusted our model parameters using the standardized incidence ratio (SIR) of colorectal cancer observed in a Dutch cohort of Hodgkin lymphoma survivors. Those rates detected a 3.0-fold increased risk of developing colorectal cancer for Hodgkin lymphoma survivors (regardless of the Hodgkin lymphoma treatment strategy, but treatment included IRT and/or procarbazine-containing chemotherapy) compared with the general population (1). The MISCAN-Colon model specifically simulates the adenoma–carcinoma sequence (14, 15), and does not directly simulate serrated lesions. In the current study, we assumed that the progression times from adenoma onset to colorectal cancer progression among Hodgkin lymphoma survivors were comparable with the general population. However, adenomas were assumed to be more often located in the proximal colon as seen in the cohort of Dutch Hodgkin lymphoma survivors. Our model assumptions (for the natural history of colorectal cancer) were tested replicating observed Dutch and worldwide data on Hodgkin lymphoma survivors (Supplementary Figs. S1 and S2; refs. 6, 16). In this modelling exercise (model validation), we tested both assumptions related to the causes of the higher colorectal cancer risk [as consequence of a higher onset of adenoma (base case analysis) versus as consequence of a combination of higher adenoma onset and faster progression from adenoma to carcinoma (sensitivity analysis)] as described in the Methods of our study. The results of the stool tests (FIT and Mt-sDNA) were based on a prospective study, which evaluated the diagnostic accuracy in Hodgkin lymphoma survivors (9).

Adjustments to reflect the Hodgkin lymphoma population: 3 cohorts

Briefly, we used the SIR of colorectal cancer observed in a Dutch cohort of 5-year Hodgkin lymphoma survivors to assume a 3.0-fold increased risk of colorectal cancer in Hodgkin lymphoma survivors (for the entire cohort including all Hodgkin lymphoma treatment strategies including IRT and/or procarbazine-containing chemotherapy) compared with the general population (**Fig. 1**; ref. 1). We did not assume changes in risk over calendar time. In our model, we assumed that the higher colorectal cancer risk was a consequence of a higher incidence of adenomas. We assumed the same adenoma incidence as the Dutch general population before Hodgkin lymphoma diagnosis and treatment (from age 0–24 years), and increased adenoma incidence after that. Model validations are reported in Supplementary Document (Supplementary Figs. S1 and S2). We also adjusted the model to consider the 5.2 times higher risk of death for all causes (excluding anal and colorectal cancer mortality) observed among Hodgkin lymphoma survivors (compared with the general population in same age, gender, and calendar period; ref. 7).

The different treatment strategies for Hodgkin lymphoma resulted in different SIRs for developing colorectal cancer (1). Compared with the general population, Hodgkin lymphoma survivors treated with procarbazine without IRT had a 2.0-fold higher SIR for colorectal cancer, whereas in those treated with IRT and procarbazine the risk was 5.7-fold higher (1). We, therefore, also performed separate analyses considering differences in colorectal cancer risk based on Hodgkin lymphoma treatment (increasing or decreasing the risk accordingly). In those analyses, we assumed no difference in all-cause mortality by Hodgkin lymphoma treatment (i.e., 5.2-fold higher than the general population; ref. 7). Validation of these two separate model versions was performed and reported in **Fig. 1**.

Surveillance strategies simulated

We performed a cost-effectiveness analysis for each Hodgkin lymphoma survivor group to explore possible reasonable options to determine the most optimal surveillance strategy. We evaluated benefits and costs of 90 different surveillance strategies (including no surveillance) varying in test modality (colonoscopy, FIT with different positivity cutoffs, or mt-sDNA), age to start (35, 40, 45, 50 years), intervals (3, 5, and 10 years for colonoscopy, and 1 and 2 years for stool tests), and age to end (70 or 75 years). These variations were evaluated to determine the most beneficial strategy for the different subgroups. Test characteristics of the stool tests for detecting advanced neoplasia

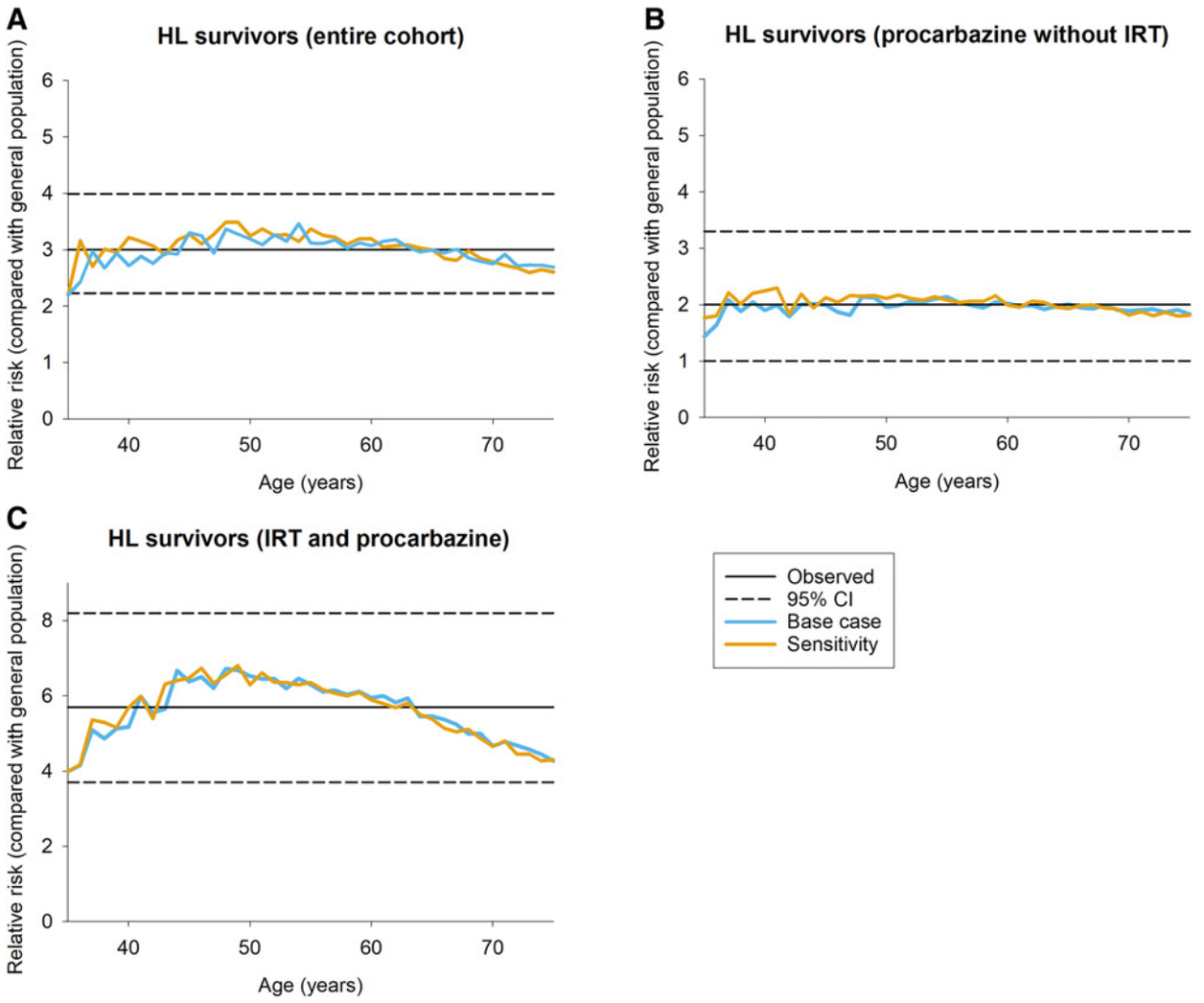

Figure 1.

Simulated and expected adenoma prevalence and relative risks for colorectal cancer (compared with average risk individuals) among Hodgkin lymphoma (HL) survivors. This figure represents the validation of the data of HL survivors against published data for the entire cohort (**A**), HL survivors treated with procarbazine without IRT (**B**) and HL survivors treated with IRT and procarbazine (**C**). Simulated outcomes were computed assuming no surveillance.

were based on diagnostic analysis previously performed in Hodgkin lymphoma survivors treated with IRT and/or procarbazine-containing chemotherapy who prospectively underwent a colonoscopy and performed stool tests prior to colonoscopy (**Table 1**; ref. 9). For FIT (OC-Sensor, Eiken Chemical, Tokyo, Japan), three different predetermined cutoffs were evaluated, specifically 10, 20, 47 μg Hb/g feces. The positivity at the mt-sDNA test (Cologuard, Exact Sciences Corporation, Madison, United States) was classified as described in previous studies (9, 17). Participants with a positive stool test were simulated to undergo a colonoscopy (6). We assumed that the completion rate of colonoscopy was 100% and the complication rate was similar to the general population. We assumed 100% participation in all surveillance and diagnostic follow-up.

Costs

We applied a modified societal perspective for the cost-effectiveness analysis, including patient time costs but no other indirect costs (i.e., traveling). Cost for colonoscopy and FIT surveillance has been informed from the monitoring report of the Dutch FIT organized screening programme (18). As information on the cost for the mt-sDNA test are lacking in the Netherlands, we assumed the maximum out-of-pocket cost ($649, 2017) of Cologuard in U.S. market (19, 20). Costs for treatment and care of colorectal cancer have previously been published (21). All costs were updated to the year 2019 using the cost price index from the Dutch Health Care Authority (22).

Outcomes

We simulated three cohorts of 10 million Hodgkin lymphoma survivors aged 35 years old in 2019 (with Hodgkin lymphoma diagnosed at age of 25 years) for the three treatment categories (entire cohort of Hodgkin lymphoma survivors including all Hodgkin lymphoma treatment strategies, Hodgkin lymphoma survivors treated with procarbazine without IRT, and Hodgkin lymphoma survivors

Table 1. Key modelling assumptions.

Input parameter	Model assumptions	One-way sensitivity analyses
Demography		
All-cause mortality	Dutch lifetables (2016; ref. 43), adjusted assuming 5.2-fold increased all-cause mortality in Hodgkin lymphoma survivors	**1.** Dutch lifetables (2016; ref. 43), adjusted assuming the following increased risks in all-cause mortality according years since Hodgkin lymphoma diagnosis: (25) 10–14 years: RR = 7.2 15–19 years: RR = 4.7 20–24 years: RR = 4.3 25–29 years: RR = 5.0 ≥30 years: RR = 6.9 **2.** Dutch lifetables (2016; ref. 43), adjusted assuming 3.12-fold increased all-cause mortality in Hodgkin lymphoma survivors (26)
Natural history		
Adenoma onset	Age-dependent (nonhomogeneous Poisson) with more frequent adenoma (assumed after diagnosis of Hodgkin lymphoma, age 25 years) adjusted according to colorectal cancer risks observed in Hodgkin lymphoma survivors:Entire cohort of Hodgkin lymphoma survivors: RR = 3.4^{λ};Hodgkin lymphoma survivors with IRT + Procarbazine: RR = 7.12^{λ};Hodgkin lymphoma survivors treated with procarbazine without IRT: RR = 2.1^{λ}.	**3.** Entire cohort of Hodgkin lymphoma survivors combined: RR = 1.75^{λ};Hodgkin lymphoma survivors with IRT + Procarbazine: RR = 3.65^{λ};Hodgkin lymphoma survivors treated with procarbazine without IRT: RR = 1.1^{λ}. Assuming a shorter adenoma state duration compared with the general population: Exp $(\lambda = 70)^{\lambda}$ **4.** According to Rigter and colleagues (2019), Supplementary Fig. S2:Entire cohort of Hodgkin lymphoma survivors: RR = 4.85^{λ}; Hodgkin lymphoma survivors with IRT + Procarbazine: RR = 7.16^{λ};Hodgkin lymphoma survivors treated with procarbazine without IRT: RR = 3.1^{λ}
Adenoma localization	Rectum: 7.9%; Sigmoid: 11.45%; Descending:10.75%; Transverse: 31.85%; Ascending: 26.05%; and Cecum:12% (6)	**5.** Rectum: 26.38%; Rectosigmoid: 9.12%; Sigmoid: 26.37%; Descending:6%; Transverse: 9.01%; Ascending: 8.85%; and Cecum:14.27% (29)
Adenoma progression		
State transitions	Age-dependent	
State durations, years (total)	Exp$(\lambda = 140)^{\lambda}$	See 3.
Cancer progression (preclinical)		
Stage transitions	Age-dependent	
Stage durations, years	Exp$(\lambda = 2.5)$	
Colorectal cancer survival	Age-/Stage-/Localization-dependent	**6.** 1.33-fold lower compared with Dutch general population with a colorectal cancer diagnosis (27)
FIT and sMT-DNA performance		

Sensitivity***, %	FIT 10 µg Hb/g feces	FIT 20µg Hb/g feces	FIT 47 µg Hb/g feces	MT-sDNA
adenomas <10mm	0	0	0	0
adenomas ≥10mm	26.5	18.5	12.6	31.1
malignant neoplasia (early) §§[29]	65	52.5	50	97
malignant neoplasia (late) §§[29]	90	83.5	82.5	86
Specificity, %	91	95	96	62

7. Systematic FIT negative results were assumed (28)

8. Sensitivity for adenomas (6–9mm, %; ref. 29):
10 µg Hb/g feces = 9.6;
20 µg Hb/g feces = 4.4;
47µg Hb/g feces = 2.5.

(Continued on the following page)

Table 1. Key modelling assumptions. (Cont'd)

Input parameter	Model assumptions	One-way sensitivity analyses
Colonoscopy performance		
Sensitivity[†], %		
adenomas 0–5mm	75	
adenomas 6–9mm	85	
adenomas ≥10mm	95	
malignant neoplasia	95	
Specificity[‡], %	86	
Complete colonoscopy examination, %	100 (6)	**9.** 92 (29)
Complication rates, % with polypectomy[§]	Age-dependent	
Fatal complications[‖]	0.000329	
without polypectomy	-	
Costs,[¶]		
FIT	15	
sMT-DNA	604[*]	
Colonoscopy		
with polypectomy	887	
without polypectomy	679	
Complications[#,**,††]	3,488	
Per life-year with cancer care		
Initial year, stage I–IV	15,222–30,444	**10–11.** 50% higher and 100% higher
Ongoing, stage I–IV	414	
Terminal year (colorectal cancer death), stage I-IV	21,311–30,444	
Terminal year (other causes), stage I–IV	5,358–17,049	
Discounting rates (Cost-effectiveness analysis)		**12.**
Benefits	3%	1.5%
Costs	3%	4%

Abbreviation: RR, relative risk.

[λ] The combination of increased adenoma onset and short adenoma state duration resulted in a risk of colorectal cancer (compared with Dutch general population), respectively, of 3.0-fold higher in the entire cohort of Hodgkin lymphoma survivors, 2.0-fold in Hodgkin lymphoma survivors treated with procarbazine without IRT, and 5.7-fold in Hodgkin lymphoma survivors treated with IRT and procarbazine (**Fig. 1**; ref. 6).

[†]The sensitivity of colonoscopy for the detection of adenomas and colorectal cancer within the reach of the endoscope was obtained from a systematic review on miss rates seen in tandem colonoscopy studies (44).

[‡]Specificity for colonoscopy is therefore based on an adenoma prevalence study of patients undergoing surveillance colonoscopy (45).

[§]Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren and colleagues (46).

[‖]The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren and colleagues (46) by the risk for death given a perforation obtained from a study by Gatto and colleagues (47).

Costs are presented in Euro.

[#]Serious gastrointestinal (GI) complications included perforations, gastrointestinal bleeding, or transfusions.

[**]Other gastrointestinal (GI) complications included paralytic ileus, nausea and vomiting, dehydration, or abdominal pain.

[††]Cardiovascular complications included myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock.

[§§]FIT sensitivity for malignant neoplasia were informed using the study of Goede SL and colleagues (2013). For FIT 47 μg Hb/g feces those sensitivity values were assumed equal to those provided for FIT 40 μg Hb/g feces. (29).

[*]maximum reimbursement cost in US as assumed in Lew and colleagues (2018) IJC (20).

[***]Sensitivities were per-lesion.

treated with IRT and procarbazine). We simulated three cohorts of individuals all born in the same year. Although the actual number of Hodgkin lymphoma survivors in the Netherlands evidently is not in that order of magnitude (8, 11), the large cohort sample size was chosen to guarantee stable model outcomes in our simulations. To endorse generalizability to Hodgkin lymphoma survivor populations of different sizes all outcomes are reported per 1.000 survivors aged 35 years in 2019. Age 35 was chosen because the simulated increase in adenoma incidence from age 25 years onwards would require at least 10 years for these adenomas (caused by Hodgkin lymphoma treatment) to result in an increase in colorectal cancer incidence. As the information used to inform the model was limited, the increase in the adenoma incidence was assumed to not change according to period of Hodgkin lymphoma diagnosis.

For each surveillance strategy, the surveillance effectiveness [i.e., number of colorectal cancer deaths prevented, relative colorectal cancer mortality reduction and life-years gained (LYG)] and resources (colonoscopies, FIT, mt-sDNA test and cost) were analyzed, discounting the LYG and cost at the conventional 3% annual discount rate (Supplementary Tables S1–S3). We calculated the number of colonoscopies needed to prevent a colorectal cancer death by dividing the total number of colonoscopies performed (per 1,000) by the number of colorectal cancer deaths prevented per 1,000 Hodgkin lymphoma survivors screened, referred to as number needed to screen (NNS, Supplementary Tables S4–S6). For each group of Hodgkin lymphoma survivors, we also predicted colorectal cancer deaths and total costs simulating two existing surveillance recommendations indicated in the Netherlands: (i) the screening strategy for the Dutch general

population (biennial FIT, i.e., once every 2 years, from age 55 to 75 years, 47 μg Hb/g feces); and (ii) the surveillance strategy for individuals with a family history of colorectal cancer (colonoscopy surveillance repeated every 5 years from age 45–75 years).

Cost-effectiveness analyses

The optimal colorectal cancer surveillance strategy in Hodgkin lymphoma survivors was determined by first excluding strategies that were more expensive and less effective than (combinations of) other simulated strategies (23). For the remaining strategies (defined as 'efficient strategies'), we calculated the incremental cost-effectiveness ratio (ICER) by comparing the ratio between additional costs and LYG to the next less expensive efficient strategy. The optimal strategy was defined as the most effective strategy with an ICER below the willingness-to-pay threshold of €20,000 per LYG (21, 24). Strategies with an ICER exceeding €20,000 were considered not cost-effective. A separate analysis was performed excluding the stool tests to evaluate which colonoscopy surveillance program was most cost-effective (results reported and discussed in the Supplementary Methods and Supplementary Tables S7–S9).

Sensitivity analyses

Multiple one-way sensitivity analyses were performed to reinforce the results under a variety of assumptions (**Table 1**). Those assumptions included an adjustment in the lifetables including different relative risks for different intervals after Hodgkin lymphoma treatment (25); another adjustment in the lifetables based on Anderson et al (26); higher colorectal cancer risk as shown in a prospective study in which Hodgkin lymphoma survivors underwent a colonoscopy and a higher prevalence of advanced neoplasia was detected; Supplementary Fig. S2 (6); different colorectal cancer localization (in line with the general Dutch population; ref. 6); a 1.33 lower colorectal cancer relative survival (27); systematic FIT negative results (28); FIT sensitivity for medium adenomas (6–9 mm) assumed as reported for the Dutch general population (29); a different assumption for the pathway to higher colorectal cancer risk in Hodgkin lymphoma survivors (colorectal cancer risk caused by a higher adenoma onset in combination with a twice-faster adenoma progression; **Fig. 1**); a lower complete colonoscopy examination rate (92% instead of 100%); higher costs for colorectal cancer treatment and care (50% and 100% higher); and 4% discount rate for costs and 1.5% for benefits as recommended by the Dutch Ministry of Health (30).

Data availability

The data generated in this study are available within the article and its Supplementary Data files. Detailed data generated in this study about the MISCAN model is available upon request from the corresponding author.

Results

In the entire Hodgkin lymphoma survivor cohort (not stratified by Hodgkin lymphoma treatment), 26 colorectal cancer deaths per 1000 Hodgkin lymphoma survivors (starting aged 35 years in 2019) were predicted over a lifetime in the absence of surveillance (**Table 2**). Up to 49% of those colorectal cancer deaths may be averted with the recommended screening strategy for the Dutch general population (**Fig. 2**) with biennial FIT 47 μg Hb/g feces between 55 to 75 years of age at the total costs of € 1.1 million per 1,000 Hodgkin lymphoma survivors (NNS = 75, data not included). The surveillance strategy indicated for individuals with family history of colorectal cancer being primary colonoscopy surveillance from age 45 years can prevent up to 80% of colorectal cancer mortality in Hodgkin lymphoma survivors, however, at higher costs (total costs €2.4 million per 1,000 Hodgkin lymphoma survivors, NNS = 222). The most optimal cost-effective colorectal cancer surveillance strategy was annual FIT surveillance from age 45 to 70 years using a positivity cut-off threshold of 47 μg Hb/g feces, which prevented up to 70% of colorectal cancer mortality, however, at lower costs than the previous colonoscopy strategy (compared with no surveillance; total costs € 1.4 million per 1,000 Hodgkin lymphoma survivors; NNS = 75; ICER = €18,000 per LYG; **Fig. 3**, **Table 2**, and Supplementary Table S4 and S10).

For Hodgkin lymphoma survivors treated with procarbazine without IRT, the model predicted 17 colorectal cancer deaths per 1,000 Hodgkin lymphoma survivors without surveillance. Up to 47% of those deaths could be prevented with the colorectal cancer screening strategy adopted for the Dutch general population (biennial FIT at cutoff 47 55 from age 75 years, total costs €0.8 million per 1,000 Hodgkin lymphoma survivors, NNS = 60, data not included); whereas 80% could be avoided by primary colonoscopy surveillance with a starting age of 45 years, however, at higher costs (total costs = €2.2 million per 1,000 Hodgkin lymphoma survivors, NNS = 336; **Fig. 2**). However, we found that biennial FIT surveillance (47 μg Hb/g feces) from age 45 and 70 years was the optimal strategy, preventing 56% of colorectal cancer mortality (compared with no surveillance) at an acceptable cost of €15,000/LYG (total costs = € 0.9 million per 1,000 Hodgkin lymphoma survivors; NNS = 79; **Fig. 3**, **Table 2**, and Supplementary Table S5 and S11).

In Hodgkin lymphoma survivors treated with IRT and procarbazine, 47 colorectal cancer deaths (per 1,000 Hodgkin lymphoma) were predicted without surveillance. Screening as suggested for the Dutch general population may prevent up to 50% of those deaths (at the costs €1.9 million per 1,000 Hodgkin lymphoma survivors, NNS = 32, data not included); whereas surveillance recommended for individuals with family history of colorectal cancer prevented up to 81% of colorectal cancer (at the cost of €2.8 million per 1,000 Hodgkin lymphoma survivors, NNS = 124; **Fig. 2**). Nevertheless, annual FIT surveillance (47 μg Hb/g feces) from age 40 and 70 years was optimal, averting 75% of colorectal cancer mortality (compared with no surveillance; total costs = € 2.2 million per 1,000 Hodgkin lymphoma survivors; ICER = €13,000 per LYG; NNS = 56; **Fig. 3**, **Table 2**, and Supplementary Table S6 and S12).

For each group of Hodgkin lymphoma survivors, colonoscopy surveillance was estimated not to be cost-effective in comparison with FIT (Supplementary Table S7–S9). Separate analyses were performed excluding stool test surveillance and only including colonoscopy surveillance. This analysis is described in Supplementary Methods and Supplementary Tables S7–S9.

Sensitivity analysis

In all sensitivity analyses, FIT surveillance was most cost-effective for all Hodgkin lymphoma treatment strategies. The optimal cutoff for FIT was quite sensitive to model assumptions. The optimal cutoff changed to a lower cutoff in 31% of the sensitivity analyses. This included among others the analyses which assumed: (i) higher all-cause mortality in the entire Hodgkin lymphoma cohort, (ii) the same FIT sensitivity for medium adenomas as in the general population, and (iii) higher colorectal cancer treatment costs (**Table 3**). The age range was quite robust, and only changed in the two sensitivity analyses that assumed: (i) a higher colorectal cancer risk in Hodgkin lymphoma survivors, and (ii) the Dutch discounting factors for the entire cohort.

Table 2: Efficient surveillance strategies among Hodgkin lymphoma survivors per primary cancer treatment (base case analysis).

	Outcomes per 1,000 Hodgkin lymphoma survivors free of colorectal cancer diagnosis and aged 35 years in 2019 (3%)*												Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Compl.**	**Colorectal cancers†**	**Colorectal cancer deaths†**	**Colorectal cancer care**	**LYG‡**	**Total costs**	**Net costs‡**	**Incidence (%)‡**	**Mortality (%)‡**	**ICER (*1,000)**
Entire cohort of Hodgkin lymphoma survivors															
No Surveillance	0	0	33	0	33	0	73	26	214	0	966	0	0	0	0
FIT47, 50–70, 2 years	3,457	0	199	145	344	2	63	12	274	38	1,161	196	13	54	5
FIT47, 45–70, 2 years	4,936	0	254	198	452	2	60	11	273	46	1,224	258	18	59	8
FIT20, 45–70, 2 years	4,779	0	342	258	599	3	54	10	253	49	1,271	306	26	63	13
FIT47, 45–70, 1 years	**8,957**	**0**	**408**	**293**	**701**	**3**	**51**	**8**	**254**	**55**	**1,373**	**407**	**30**	**70**	**18**
FIT47, 40–70, 1 years	12,490	0	536	361	897	3	49	7	246	61	1,537	571	33	72	29
FIT20, 40–70, 1 years	11,975	0	740	447	1,187	4	43	7	220	64	1,681	716	41	75	53
FIT20, 35–70, 1 years	16,252	0	976	510	1,486	4	42	6	214	67	1,943	978	42	76	75
FIT20, 35–75, 1 years	16,611	0	997	511	1,508	4	43	6	215	67	1,967	1,001	42	78	87
FIT10, 35–70, 1 years	15,462	0	1,491	634	2,125	5	37	5	188	70	2,339	1,374	49	79	130
FIT10, 35–75, 1 years	15,809	0	1,523	634	2,158	5	37	5	189	70	2,370	1,405	49	80	148
COL, 35–70, 3 years	0	4,864	3	1,956	6,822	9	22	3	112	80	5,337	4,371	70	88	308
COL, 35–75, 3 years	0	5,003	2	1,956	6,960	9	21	3	112	80	5,437	4,471	71	89	439
Hodgkin lymphoma survivors treated with procarbazine without IRT															
No Surveillance	0	0	22	0	22	0	49	17	141	0	637	0	0	0	0
FIT47, 50–70, 2 years	3,568	0	183	108	291	1	44	8	184	23	847	210	11	52	9
FIT47, 45–70, 2 years	**5,075**	**0**	**240**	**147**	**387**	**2**	**42**	**8**	**183**	**28**	**916**	**279**	**15**	**56**	**15**
FIT20, 45–70, 2 years	4,945	0	331	194	525	2	38	7	170	30	977	339	23	61	25
FIT47, 45–70, 1 years	9,340	0	402	222	623	2	36	6	171	35	1,091	453	27	68	28
FIT47, 40–70, 1 years	12,963	0	535	273	808	2	34	5	167	38	1,257	620	30	70	45
FIT47, 40–75, 1 years	13,362	0	550	274	825	3	35	5	169	39	1,279	642	29	72	71
FIT20, 40–70, 1 years	12,528	0	753	343	1,096	3	30	5	149	40	1,418	781	39	74	88
FIT47, 35–75, 1 years	17,784	0	713	314	1,027	3	34	5	166	41	1,479	842	31	74	91
FIT20, 35–75, 1 years	17,273	0	1,018	393	1,411	3	29	4	146	43	1,705	1,068	40	77	115
FIT10, 35–70, 1 years	16,223	0	1,550	494	2,043	4	25	4	127	45	2,103	1,465	49	79	182
FIT10, 35–75, 1 years	16,597	0	1,585	494	2,079	4	25	3	127	45	2,135	1,498	49	80	191
COL, 35–70, 3 years	0	5,209	2	1,611	6,822	7	14	2	73	52	5,176	4,539	72	88	461
COL, 35–75, 3 years	0	5,359	1	1,611	6,972	8	14	2	73	52	5,284	4,647	72	90	623
Hodgkin lymphoma survivors treated with IRT and procarbazine chemotherapy															
No Surveillance	0	0	59	0	59	1	127	47	392	0	1,753	0	0	0	0
FIT20, 50–70, 2 years	3,094	0	291	282	573	3	96	18	463	81	1,867	113	24	61	1
FIT20, 45–70, 2 years	4,465	0	367	387	754	4	90	16	451	100	1,929	175	29	67	3
FIT10, 45–70, 2 years	4,197	0	501	494	995	5	80	13	419	108	1,998	244	37	72	8
FIT47, 45–70, 1 years	8,255	0	426	434	860	4	85	13	451	109	2,006	253	33	72	10
FIT47, 40–70, 1 years	**11,623**	**0**	**545**	**540**	**1,086**	**5**	**81**	**12**	**435**	**121**	**2,156**	**403**	**36**	**75**	**13**
FIT20, 40–70, 1 years	10,997	0	723	655	1,378	5	72	11	391	125	2,268	515	43	77	25
FIT20, 35–70, 1 years	15,099	0	945	753	1,698	6	70	10	377	132	2,528	774	45	78	41
FIT20, 35–75, 1 years	15,414	0	963	754	1,717	6	70	10	378	132	2,549	796	44	79	69
FIT10, 35–70, 1 years	14,131	0	1,393	916	2,309	7	63	9	336	137	2,877	1,123	50	80	73
FIT10, 35–75, 1 years	14,436	0	1,422	916	2,338	7	63	9	337	137	2,904	1,151	50	81	115
COL, 35–70, 3 years	0	4,289	5	2,516	6,810	11	41	6	217	153	5,700	3,947	68	88	173
COL, 35–75, 3 years	0	4,410	4	2,516	6,930	12	40	5	218	153	5,787	4,034	68	89	283

Abbreviation: COLs = colonoscopies.

†Colorectal cancer cases and colorectal cancer death were not discounted.

‡Compared with no surveillance.

*Full participation in surveillance and post-colonoscopy surveillance was assumed. Optimal surveillance strategies were reported in bold.

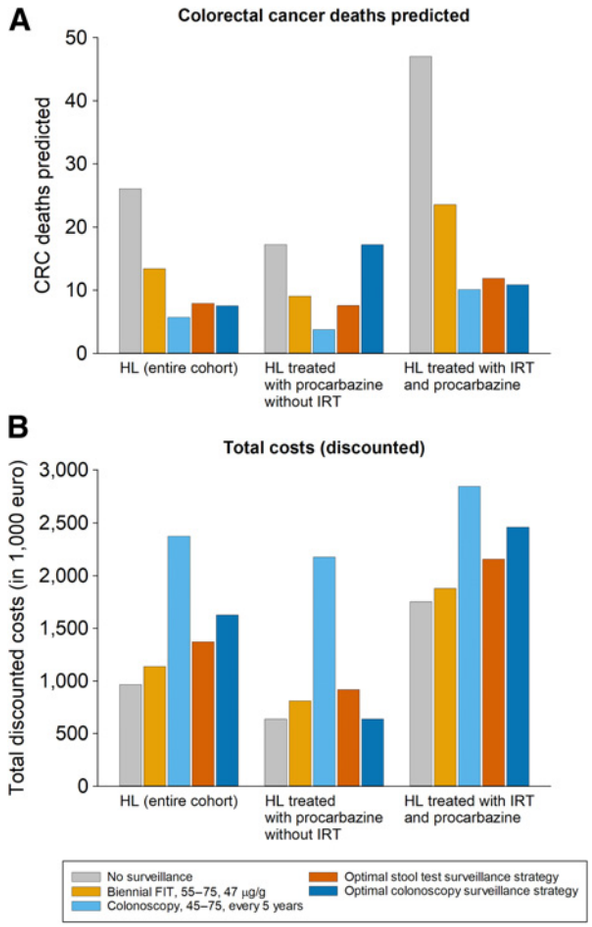

Figure 2.

Colorectal cancer (CRC) deaths and total costs per 1,000 Hodgkin lymphoma (HL) survivors aged 35 years old in 2019 under different surveillance scenarios. The CRC deaths and the total costs per 1,000 HL survivors are shown for the three subgroups of HL survivors (**A** and **B,** respectively). The figures display the different optimal surveillance strategies for the entire cohort, HL survivors treated with procarbazine without IRT and HL survivors treated with IRT and procarbazine. The different colors represent the most optimal surveillance strategies for the different HL subgroups as determined in **Table 2**. Optimal colonoscopy surveillance strategies were determined in Supplementary Tables 7–10. A willingness-to-pay threshold of €20,000 per LYG was assumed in determining the optimal surveillance strategy in each group. COL, colonoscopy.

The most cost-effective interval changed in a few sensitivity analyses (**Table 3**).

Discussion

Recent studies have suggested that Hodgkin lymphoma survivors, who received IRT, procarbazine-containing chemotherapy or both, should undergo colorectal cancer surveillance at an earlier age than recommended in population screening programs due to their increased risk of developing colorectal cancer before age 55 (1–4) and the high prevalence of colonic advanced neoplasia already at young ages (6). Using an established micro-simulation model, we found that FIT is the most cost-effective colorectal cancer surveillance strategy in this population, regardless of the Hodgkin lymphoma treatment associated colorectal cancer risk. Depending on the Hodgkin lymphoma treatment, the optimal age of commencing surveillance ranged from 40 to 45 years, which is earlier than practiced in most colorectal cancer screening programs. We showed that the optimal FIT positivity cutoff was 47 µg Hb/g feces when offering FIT annually to Hodgkin lymphoma survivors in general (the entire cohort) or to those treated with IRT and procarbazine. This FIT positivity cutoff is also used in the Dutch colorectal cancer screening programme for the average-risk population where, however, FIT is offered biennially. For those Hodgkin lymphoma survivors treated with procarbazine without IRT (patients at lower colorectal cancer risk than those with additional IRT) the same program as for the general population would be beneficial, only with a starting age at 45 (biennially and FIT positivity cutoff (47 µg Hb/g feces).

The earlier optimal age of surveillance invitation reflects the higher risk of colorectal cancer among Hodgkin lymphoma survivors at a younger age (1, 2, 6, 31) and is in line with the increased risk after 10 to over 30 years from Hodgkin lymphoma treatment (at a median age of 27 years; ref. 1). Moreover, our model shows that surveillance for Hodgkin lymphoma survivors could stop at age 70 years, 5 years earlier than recommended in most (European) colorectal cancer screening programs (75 years). This can be related to the high all-cause mortality observed among Hodgkin lymphoma survivors (7, 26). In Hodgkin lymphoma survivors, performing surveillance at an older age might directly result in colorectal cancer overdiagnosis and overtreatment with no improvement of life expectancy (no colorectal cancer death averted).

In line with previous studies on the cost-effectiveness of mt-sDNA in the asymptomatic population (32–35), we found that mt-sDNA was not cost-effective compared with other modalities. Although mt-sDNA was estimated to reduce colorectal cancer incidence and mortality, it was an inefficient surveillance option (less effective and higher costs; ref. 32).

This study has several limitations. Firstly, the MISCAN model assumes that all colorectal cancers arise through a traditional adenoma–carcinoma sequence, and the pathway of development of serrated polyps is not (yet) included in MISCAN. To avoid bias towards FIT surveillance, which is less sensitive for serrated lesions than mt-sDNA (9, 17, 36), we have modelled advanced serrated lesions as large adenomas, assuming the same progression rate for both types of lesions. Previously, in the prospective colonoscopy study, we detected significantly more advanced serrated polyps and serrated polyposis syndrome in Hodgkin lymphoma survivors compared with the general population (6), which may have impact on our model adjustments even though the colorectal cancer risk was considered. As we could not disentangle those colonoscopy results to correctly inform our current model structure, we decided to consider the advanced serrated lesions as advanced adenomas. With this assumption, we could compute the adenoma prevalence in Hodgkin lymphoma survivors in way which allow us to validate the model (Supplementary Fig. S2). Furthermore, by applying FIT parameters computed from data which include both adenomas and serrated lesions in Hodgkin lymphoma survivors, our model results were indirectly adjusted to account the potential presence of serrated lesions. A second limitation is that we cannot inform sensitivity of the FIT and mt-sDNA for colorectal cancer based on the prospective data in Hodgkin lymphoma survivors, because no colorectal cancer was detected in this cohort, only precursor lesions (6, 9). Thus, colorectal cancer sensitivity model parameters were based on data from the average-risk population (29). Furthermore, even for precursor lesions, the sample size was small for evaluating the stool test sensitivity (9). Moreover, the exact pathogenesis of colorectal cancer

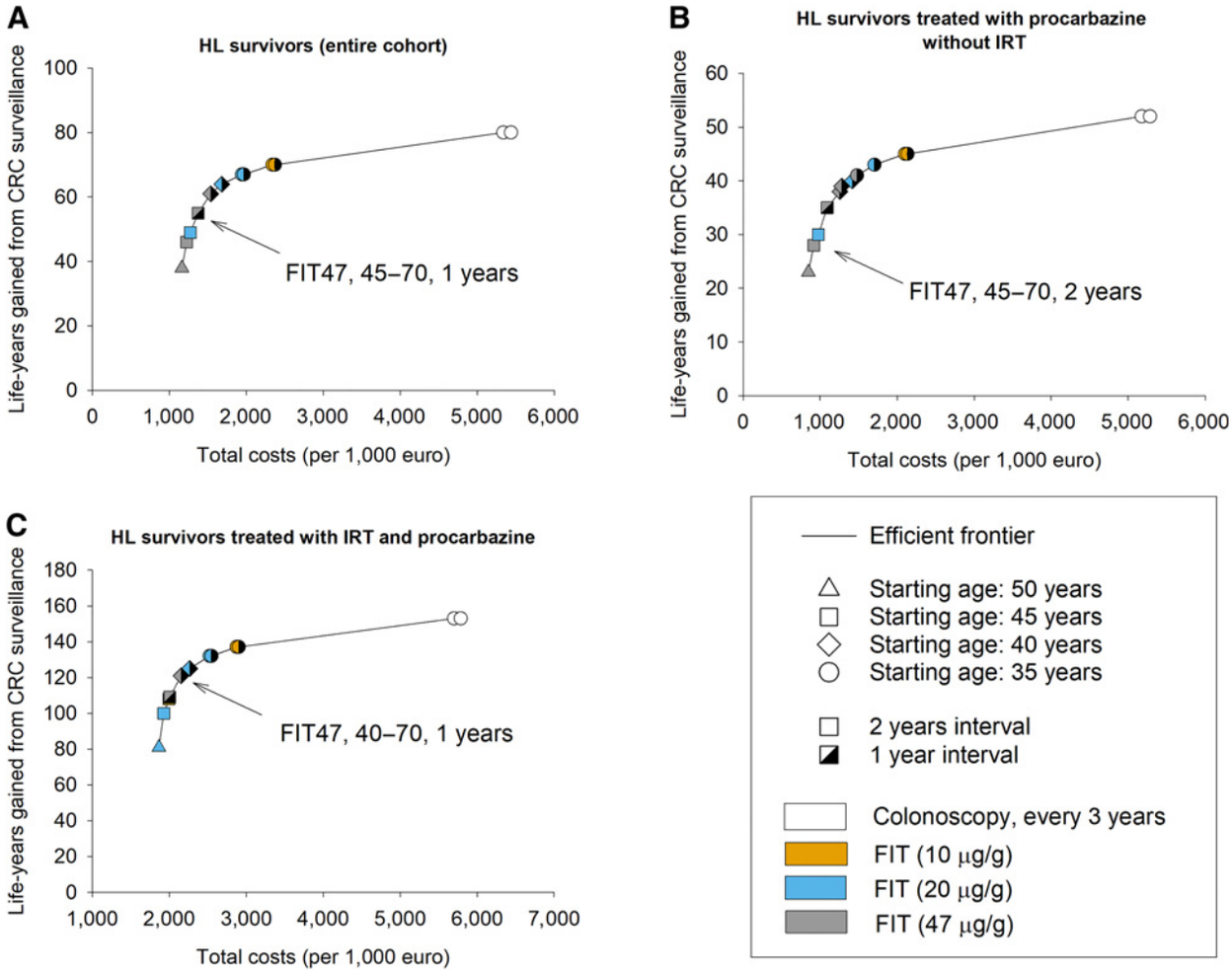

Figure 3.

Efficient frontier with efficient surveillance strategies for Hodgkin lymphoma (HL) survivors. In this efficient frontier displays the LYG from CRC surveillance against the total costs per 1,000 euro. Total costs and LYG from surveillance were discounted (3% discounting rate) and 100% adherence was assumed for surveillance and diagnostic test. The optimal surveillance strategies are labelled an indicated by arrows. The efficient frontier is shown separately for the entire cohort (**A**), HL survivors treated with procarbazine chemotherapy without IRT (**B**), and HL survivors treated with IRT and procarbazine chemotherapy (**C**). CRC, colorectal cancer.

in Hodgkin lymphoma survivors remains unknown. Previous research by our group detected a higher prevalence of microsatellite instability colorectal cancer in Hodgkin lymphoma survivors due to double somatic mutations in mismatch-repair genes (37), suggesting a faster progression from precursor lesions to colorectal cancer (38). Hence, we performed a specific sensitivity analysis assuming faster progression from adenoma to colorectal cancer in Hodgkin lymphoma survivors. We found that the optimal surveillance strategy was not sensitive to this assumption. Furthermore, we assumed full adherence to follow-up and surveillance procedures because this provides unbiased estimates for optimal surveillance strategies. Results should therefore be used to guide policy, but not to take these results as the estimated impact of that policy. In practice, adherence to surveillance is usually lower, resulting in a lower impact of surveillance than suggested. When imperfect adherence is assumed, this would result in strategies with short intervals and larger age target to compensate for the suboptimal surveillance. This would result in Hodgkin lymphoma survivors who adhere to surveillance to be over-screened. If only 41% of the population would participate, the costs, benefits, and harms of the program would decrease proportionally. Considering the low uptake of colonoscopy screening observed among childhood cancer survivors in US (i.e., 11.5%; ref. 39), our findings about the benefits of FIT surveillance in Hodgkin lymphoma may have vital importance as stool tests are generally characterized by higher participation rates compared with colonoscopy (at least in the average-risk population; ref. 40). To assess the robustness of our modelling estimates, a full probabilistic sensitivity analysis was not performed as extremely resource-demanding. Thus, we focused our assessments carrying out several one-way sensitivity analyses on key specific model parameters. Finally, Hodgkin lymphoma treatment regimens have changed over the past decades with a reduction of radiotherapy volumes and doses and changes in chemotherapy regimens, although procarbazine is still used in e.g., the BEACOPP regimen (41). Hence, patients currently diagnosed with Hodgkin lymphoma might have a lower colorectal cancer risk and a less intensive surveillance could be optimal (2).

Table 3. Optimal surveillance strategies* under different sensitivity analyses.

	Hodgkin lymphoma (Entire cohort)	Hodgkin lymphoma (Procarbazine without IRT)	Hodgkin lymphoma (IRT + Procarbazine)
Basecase analysis	FIT47, 45–70, 1 year	FIT47, 45–70, 2 years	FIT47, 40–70, 1 year
Sensitivity analyses:			
1. Adjustment lifetables including different relative risks for different intervals after Hodgkin lymphoma treatment	FIT20, 45–70, 2 years	Unchanged	Unchanged
2. Adjustment in the lifetables based on other Anderson et al	Unchanged	FIT47, 45–70, 1 year	FIT20, 40–70, 1 year
3. Higher colorectal cancer risk caused by higher adenoma onset	FIT47, 40–70, 1 year	FIT47, 45–70, 1 year	Unchanged
4. Different adenoma localization	Unchanged	Unchanged	Unchanged
5. 1.33-fold higher colorectal cancer relative survival	Unchanged	Unchanged	Unchanged
6. Systematic FIT negative results	Unchanged	Unchanged	Unchanged
7. FIT sensitivity for medium adenomas (6–9 mm) as general population	Unchanged	Unchanged	FIT10, 40–70, 2 years
8. Colorectal cancer risk caused directly by a combination of higher adenoma onset and faster adenoma progression	Unchanged	Unchanged	FIT20, 40–70, 1 year
9. Lower complete colonoscopy examination rate (92%)	Unchanged	Unchanged	Unchanged
10. Higher colorectal cancer treatment costs (+50%)	FIT10, 45–70, 2 years	FIT20, 45–70, 2 years	FIT10, 40–70, 2 years
11. Higher colorectal cancer treatment costs (+100%)	FIT10, 45–70, 2 years	FIT10, 45–70, 2 years	FIT20, 40–70, 1 year
12. Discounting factor (4% costs, 1.5% benefits)	FIT47, 40–70, 1 year	FIT47, 45–70, 1 year	FIT20, 40–70, 1 year

*Assuming a willingness to pay threshold of €20,000 per LYG from surveillance.

One of the strengths of this study is that this is the first cost-effectiveness analysis of stool testing performed for Hodgkin lymphoma survivors. Our study suggests that FIT stool tests are cost-effective modalities for colorectal cancer surveillance in this known high-risk group for developing colorectal cancer. FIT is easy to perform and noninvasive. Reducing the use of colonoscopy surveillance will reduce potential harms (i.e., colonoscopy burden and complications) and be beneficial for the national healthcare system limiting the demand of colonoscopy and the workload of gastroenterologists. This will not only impact Hodgkin lymphoma survivors, but also other high-risk groups. Currently, ongoing research is aiming to evaluate whether stool test surveillance might also be beneficial in other high-risk groups (42).

Colorectal cancer surveillance in Hodgkin lymphoma survivors at increased risk for colorectal cancer (treated with IRT and/or procarbazine-containing chemotherapy) is cost-effective and should commence earlier than in the general population. For all examined Hodgkin lymphoma subgroups, FIT surveillance was the most cost-effective strategy. This implies introduction of surveillance with a modality that is currently not used for surveillance in high-risk groups but is extensively used in population-based colorectal cancer screening programs.

Authors' Disclosures

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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