Cost-Effectiveness of Colonoscopy-Based Colorectal Cancer Screening in Childhood Cancer Survivors

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ABSTRACT

Background: Childhood Cancer Survivors (CCS) are at increased risk of developing colorectal cancer (CRC) compared to the general population, especially those previously exposed to abdominal or pelvic radiation therapy (APRT). However, the benefits and costs of CRC screening in CCS are unclear. In this study, we evaluated the cost-effectiveness of early-initiated colonoscopy screening in CCS.

Methods: We adjusted a previously validated model of CRC screening in the US population (MISCAN-Colon) to reflect CRC and other-cause mortality risk in CCS. We evaluated 91 colonoscopy screening strategies varying in screening interval, age to start, and age to stop screening for all CCS combined and for those treated with or without APRT. Primary outcomes were CRC deaths averted (compared to no screening) and incremental cost-effectiveness ratios (ICERs). A willingness-to-pay threshold of $100,000 per life-year gained (LYG) was used to determine the optimal screening strategy.

Results: Compared to no screening, the US Preventive Services Task Force's average risk screening schedule prevented up to 73.2% of CRC deaths in CCS. The optimal strategy of screening every 10 years from age 40 to 60 averted 79.2% of deaths, with ICER of $67,000/LYG. Among CCS treated with APRT, colonoscopy every 10 years from age 35 to 65 was optimal (CRC deaths averted: 82.3%; ICER: $92,000/LYG), while among those not previously treated with APRT, screening from age 45 to 55 every 10 years was optimal (CRC deaths averted: 72.7%; ICER: $57,000/LYG).

Conclusions: Early initiation of colonoscopy screening for CCS is cost-effective, especially among those treated with APRT.

INTRODUCTION

With steady improvements in treatment and supportive care, survival of children diagnosed with cancer has greatly improved in recent decades.[36] However, with improved survival, childhood cancer survivors (CCS) are at increased risk of developing a second malignancy, in large part related to their treatment.[10, 260] Abdominal or pelvic radiation therapy (APRT), for example, increases risk of colorectal cancer (CRC) up to 11-fold, [9, 10, 12] and consequently, some expert panels, such as the Children's Oncology Group (COG), have recommended a more frequent and early CRC screening among CCS with this exposure.[144, 261] However, evidence on which to base specific recommendations is limited.[9] It is unclear to what extent early screening could produce a clinically meaningful reduction in CRC mortality, whether it is likely to be cost-effective, and what the optimal start age and frequency of screening are. This might in part explain why other expert groups, such as the Scottish Intercollegiate Guidelines Network and the Swedish Working Group for Long-term Follow-up after Childhood Cancer, have not recommended early initiation of CRC screening.[124, 262]

Ideally, effectiveness of CRC screening in CCS would be evaluated in a randomized clinical trial (RCT); however, no such trials are underway or likely to be initiated in the near future, and consequently, evidence to guide clinical practice will need to come from non-RCT sources. In this context, we simulated benefits and costs of CRC screening using a modeling approach and performed a cost-effectiveness analysis to determine which colonoscopy screening strategy may be optimal for this population.

MATERIALS AND METHODS

MISCAN-Colon model

For this study, we used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model (Erasmus University Medical Center, Rotterdam, The Netherlands).[242] MISCAN-Colon is a well-established stochastic microsimulation model for CRC that has been used to guide public health policy, including – as part of the Cancer Intervention and Surveillance Modelling Network (CISNET) – decision analyses for the US Preventive Services Task Force (USPSTF) and the American Cancer Society.[69, 70] The structure and underlying assumptions are described in General Appendix and previous publications.[66, 242]

Adaptations of the MISCAN-Colon model to CCS

We adjusted the existing MISCAN-Colon model used previously for the US general population to reflect CRC and other-cause mortality risk in CCS (**Table 8.1**). First, parameters of the model were calibrated to replicate the 4.2-fold higher CRC risk observed in the Childhood Cancer Survivor Study (CCSS) in which 20% of CCS were exposed to APRT

Table 8.1. Key modelling assumptions

Input parameter	Model assumptions	
	Base-case analyses	Probabilistic sensitivity analyses (CEAF), ranges *
Demography		
All-cause mortality	U.S. lifetables, adjusted using the increased age-specific SMRs observed for CCS in SEER databases: 25-34, SMR = 5.62 35-39, SMR = 4.63 40-44, SMR = 4.02 45-49, SMR = 3.92 50-54, SMR = 3.22 55-99, SMR = 3.43	Log-normal: (5.16;6.06) (4.03;5.31) (3.50;4.67) (3.32;4.59) (2.52;4.07) (2.01;5.38)
Natural history		
Adenoma onset	Age-dependent (non-homogenous Poisson) with more frequent adenoma (assumed after diagnosis of primary cancer, age 15 years) adjusted according to CRC risks observed in CCSS: All CCS combined: RR = 4.2; CCS with APRT: RR = 8.5; CCS without APRT: RR = 2.6.	Log-normal: All CCS combined (2.8;6.1) CCS with APRT (4.5;14.6) CCS without APRT (1.2;5.0)
Adenoma progression		
State transitions	Age-dependent	-
State durations, years (total)	Exp(λ=130)	-
Cancer progression (preclinical)		
Stage transitions	Age-dependent	-
Stage durations, years	Exp(λ=2.5)	-
Colorectal cancer survival	Age-/Stage-/Localization-dependent	-
Colonoscopy performance		
Sensitivity†, %		Beta:
adenomas 0-5mm	75	(68;82)
adenomas 6-9mm	85	(78;91)
adenomas ≥10mm	95	(89;97)
malignant neoplasia	95	(89;97)
Specificity‡, %	86	(75;94)
Complete colonoscopy examination, %	95	(89;97)
Complication rates, % with polypectomy[$]	Age-dependent	
Fatal complications[‖]	0.000329	Relative difference, Log-normal: (-60%; +167%)
without polypectomy	-	
Costs, US $[¶]		
Colonoscopy		

Table 8.1. Key modelling assumptions (*continued*)

Input parameter	Model assumptions	
	Base-case analyses	Probabilistic sensitivity analyses (CEAF), ranges [*]
with polypectomy	1,400	(-9%; +10%)
without polypectomy	1,700	(-9%; +10%)
Complications		
Serious# GI complications	11,200	(-18%; +22%)
Other** GI complications	7,600	(-18%; +22%)
Cardiovascular†† complications	8,500	(-18%; +22%)
Per life-year with cancer care		
Initial year, stage I-IV	36,900-78,200	(-4%; +4%)
Ongoing, stage I-IV	3,100-12,300	(-11%; +13%)
Terminal year (CRC death), stage I-IV	64,200-88,900	(-4%; +4%)
Terminal year (other causes), stage I-IV	19,400-50,200	(-17%; +21%)

[*] The range for parameter distributions is reported using the 2.5th and 97.5th percentiles. CEAF = Cost-effectiveness acceptability frontier; CCS = Childhood Cancer Survivors; SEER = Surveillance, Epidemiology, and End Results; APRT = abdominal or pelvic radiation therapy; CRC = colorectal cancer; CCSS= Childhood Cancer Survivors Study; RR = relative risk.

[†] The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates seen in tandem colonoscopy studies[77];

[‡] Specificity for colonoscopy is therefore based on an adenoma prevalence study of patients undergoing screening colonoscopy[252];

[§] Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren et al[253];

[‖] The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren et al[253] by the risk for death given a perforation obtained from a study by Gatto et al [251].

[¶] Costs are presented in 2015 U.S. dollars and include co-payments and patient time costs (i.e., the opportunity costs of spending time on screening or being treated for a complication or CRC) but do not include travel costs, costs of lost productivity, and unrelated health care and non–health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2014: $17.01/h. Cost values were estimated for the year 2014. We assumed that colonoscopies and complications used up 40 and 190 h of patient time, respectively. Patient time costs were already included in the estimates for the costs of Lys with CRC care obtained from a study by Yabroff et al[208]; All costs were adjusted for the year 2015 using the annual average Consumer Price Indexes provided by US Bureau of Labor Statistics;

[#] Serious GI complications included perforations, gastrointestinal bleeding, or transfusions;

[**] Other 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.

(**Supplementary Figure 8.1A**),[10] assuming that the higher CRC risk in CCS was caused by a predisposition to develop more adenomas.[9, 13] Further, the model was adjusted to reflect the increased overall all-cause mortality of CCS as seen in the Surveillance, Epidemiology, and End Results (SEER) program data compared to the US general population (**Supplementary Table 8.1**). No differences in CRC stage distribution and survival were assumed compared to the general population. Under these assumptions, the model replicated observed mortality estimates from SEER databases well (1973-2013; **Supplementary Figure 8.1B**), suggesting the assumptions are reasonable.

Results from CCSS also show that the higher CRC risk seen in CCS varied according to radiation therapy exposure: CCS treated and not treated with APRT were reported to have, respectively, 8.5-fold and 2.6-fold increased risk of CRC compared to the US general population.[10] Therefore, we also performed a stratified analysis, developing two additional model versions to take in account differences in CRC risk due to APRT. Because no statistically significant impact on all-cause mortality was observed by APRT,[263] we assumed no difference in life expectancy between the two groups, although higher all-cause mortality was evaluated in specific sensitivity analyses described below.

Screening strategies simulated and cost-effectiveness analyses

We simulated a cohort of 10 million CCS with first cancer diagnosed at age 15 years for each of three populations described above (CCS all combined, CCS treated, and CCS not treated with APRT). The large simulated cohort size was carried out to guarantee model outcome stability,[66] recognizing that it exceeds the actual number of CCS in the United States.[264] For each CCS population, we performed a cost-effectiveness analysis simulating benefits and costs under 91 different strategies, including no screening and colonoscopy screening with varying age to start (25, 30, 35, 40, 45, and 50 years), interval (every 3, 5, or 10 years), and age to end (55, 60, 65, 70, and 75 years).

Cost-effectiveness analysis was carried out from a modified societal perspective, including patient time costs, but excluding other indirect costs for traveling and time of work (**Supplementary Methods**).[208, 254] Screening effectiveness (ie, number of CRC deaths prevented, relative CRC mortality reduction, and life-years gained [LYG]) and resources (colonoscopies, and cost) were computed for each screening strategy, discounting the LYG and cost at the conventional 3% annual discount rate. The number of screening tests needed to prevent a CRC death were calculated by dividing the total number of colonoscopies performed (per 1000) by the number of CRC deaths prevented per 1000 CCS screened. Outcomes are reported per 1,000 CCS aged 25 years to allow for generalizability to CCS populations of different sizes. Colonoscopy characteristics and complication rates were based on studies in the general population (**Table 8.1**).[77, 251-253] We assumed 100% adherence to screening. To determine the optimal colonoscopy screening strategy in CCS, we first excluded screening strategies that were more costly and less effective than several other

strategies as described elsewhere.[265] For all remaining strategies (ie, "efficient strategies") we calculated the incremental cost-effectiveness ratio (ICER) as the ratio between additional costs and additional LYG compared to the next less expensive efficient strategy. Of those efficient strategies, we defined as the "optimal" strategy the one that prevented the most CRC deaths with an ICER below the willingness-to-pay threshold of $100,000 per LYG. Strategies with an ICER exceeding $100,000 were considered not cost-effective. For each CCS population, we also compared the predicted CRC deaths and costs associated with the identified optimal screening strategy against a selected number of alternative strategies: no screening; colonoscopy every 10 years from age 50 to 75 (colonoscopy screening strategy recommended by the USPSTF for the US general population);[266] and colonoscopy from age 30 to 75, every 5 years (recommended by the COG for childhood survivors treated with APRT).[144]

Sensitivity analyses

Multiple one-way sensitivity analyses were also carried out to assess the robustness of the results. First, separate analyses were performed for specific subtypes of CCS, including Hodgkin Lymphoma (HL) patients (5.7-fold increased CRC risk compared to US general population);[9, 10, 263, 267] Wilms tumor (WT) patients (15.5-fold increased CRC risk, first cancer diagnosis assumed at age 5 years);[10, 263] CCS treated with APRT exceeding 30 Gray in doses (10.9-fold increased CRC risk caused by both a higher rate of adenoma incidence and a faster adenoma progression);[12] base case all-cause mortality, as well as variant with up to 2.6-fold higher all-cause mortality;[263] and alternative ages at first malignancy (5 or 20 years). Details about assumptions for these CCS subtypes are provided in the **Supplementary Methods and Supplementary Figure 8.2**. Second, we assessed results under a variety of assumptions regarding CRC risk and other-cause mortality. These assumptions included 28% lower CRC survival following a diagnosis of CRC at regional or distant stage compared to CRCs diagnosed with the same corresponding stage in the US general population;[267] different mechanism for the higher CRC risk combining shorter time of adenoma progression to invasive cancer (50% reduced) and higher adenoma incidence (**Supplementary Figure 8.1A**); a lower all-cause mortality in older ages (≥ 65 years), assuming a 2-fold standardized mortality ratio compared to US general population rather than the last available value from SEER (3.4 at age 65; **Supplementary Table 8.1**); a higher all-cause mortality rate as observed in CCSS (**Supplementary Methods, Supplementary Tables 8.1 and 8.2, and Supplementary Figure 8.3**) for CCS treated with APRT;[263, 268] and higher health care expenses for conditions unrelated to CRC for CCS with averted CRC incidence or death compared to the US general population (**Supplementary Methods**).[269] Multiway probabilistic sensitivity analyses (PSA) were finally performed to assess uncertainty surrounding the optimal choices in the base case analyses, computing cost-effectiveness acceptability frontiers (CEAFs, probabilities that optimal choice is cost-effective) for the optimal strategy

and the two neighboring efficient strategies.[270] Outcomes were reassessed while randomly varying key model assumptions across 1,000 simulations (**Table 8.1**).

RESULTS

Optimal Colonoscopy Screening Strategies

Among all CCS combined (with primary malignancy occurring at age 15 years), 37 per 1,000 were predicted to die of CRC without screening (**Table 8.2;** modeled outcomes of all evaluated strategies are shown in **Supplementary Table 8.3**). Optimal results within acceptable cost levels were achieved with colonoscopy every 10 years from age 40 to 60 years, averting 79.2% of CRC mortality. This strategy required 134 colonoscopies to prevent one CRC death at a total cost of $4.2 million/1,000 CCS, for an associated ICER of $67,000 per LYG. With screening employed as currently recommended for the average-risk US general population (USPSTF, colonoscopy from age 50 to 75, every 10 years), 73.2% of CRC deaths would be averted compared to no screening.

Colonoscopy screening from age 30 to 75 years repeated every 5 years, as suggested by COG for CCS exposed to APRT, was estimated to prevent up to 84.4% of CRC mortality among CCS, but at higher total costs ($7.2 million/1,000 CCS; **Figure 8.1**). Among CCS treated with APRT, 64 per 1,000 CCS were predicted to die of CRC without screening (**Supplementary Table 8.4**). The optimal strategy for CCS treated with APRT was screening with colonoscopy from age 35 to 65 years every 10 years, averting 82.3% of CRC deaths (97 colonoscopies needed per CRC death prevented), with an overall cost of $6.3 million/1,000 CCS (ICER of $92,000/LYG; **Table 8.2**). Screening, as recommended for the general population (USPSTF), prevented 72.7% of CRC deaths compared to no screening, whereas up to 84.8% of CRC deaths were prevented by colonoscopy from age 30 to 75 repeated every 5 years (COG recommended strategy; total costs per 1,000 CCS = $8.4 million; **Figure 8.1**). Even among CCS not treated with APRT (**Supplementary Table 8.5**), earlier initiation of screening was cost-effective, with the optimal strategy being colonoscopy screening at age 45 and 55 repeated every 10 years, averting 72.7% of CRC deaths (160 colonoscopies needed per CRC death prevented; ICER of $57,000 per LYG; **Table 8.2**).

Sensitivity analyses

There were clinically important differences in the optimal screening strategy depending on initial diagnosis and APRT dose. For WT survivors, screening intensively with colonoscopy every 3 years from age 35 to 60 was optimal, preventing up to 86.2% of CRC deaths (ICER of $73,000 per LYG), whereas among HL survivors, the optimal strategy was colonoscopy from age 40 to 60 every 10 years, averting 80.2% of CRC mortality (ICER of $51,000 per LYG; **Supplementary Table 8.6 and Supplementary Figure 8.4**). Among CCS exposed to

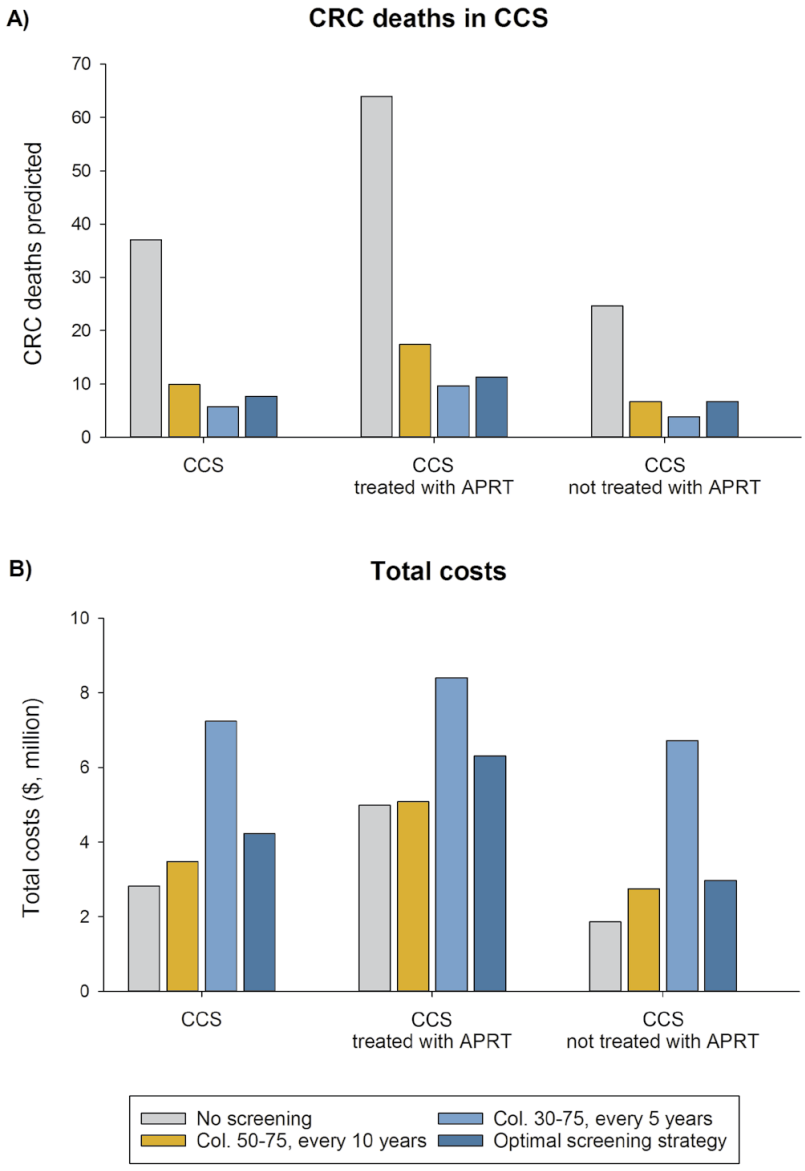


Figure 8.1. Colorectal cancer deaths and total costs ($) per 1,000 CCS aged 25 years in 2017 under different colonoscopy screening scenarios. Colorectal cancer deaths (A) and total costs (B) are shown for no screening; colonoscopy every 10 years between age 50 and 75 years (US Preventive Task Force's general population recommended colonoscopy screening strategy); colonoscopy every 5 years between age 30 and 75 years (the Children's Oncology Group colonoscopy screening indication for CCS treated with APRT); and the corresponding optimal colonoscopy screening strategy suggested by our model (CCS all combined: Colonoscopy between age 40 and 60 years every 10 years; CCS treated with APRT: colonoscopy between age 35 and 65 years every 10 years; and CCS not treated with APRT: colonoscopy between age 45 and 55 years every 10 years years). APRT = abdominal or pelvic radiation therapy; CCS = Childhood cancer survivor; Col = colonoscopy; CRC = Colorectal Cancer.

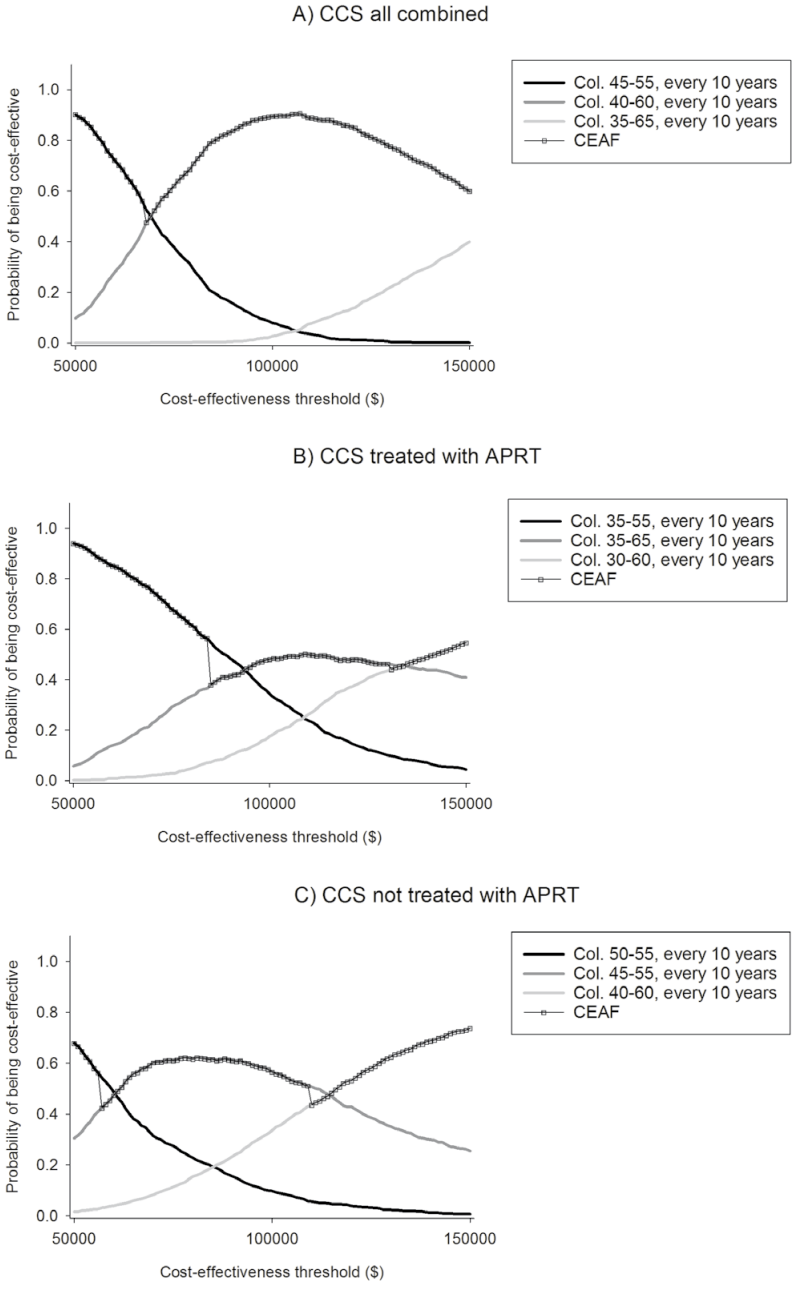


Figure 8.2. Model cost-effectiveness acceptability frontiers (CEAFs) for childhood cancer survivors (CCS) with primary cancer diagnosed at age 15 years. Results are shown for (A) all CCS; (B) CCS treated with pelvic or abdominal radiation; and (C) CCS not treated with pelvic or abdominal radiation. Uncertainty was assessed in a selected number of efficient screening strategies (the study's optimal screening strategy, the corresponding previous less costly, and the corresponding subsequent more costly strategies). CCS = Childhood cancer survivors; CEAF = cost-effectiveness acceptability frontiers; Col. = colonoscopy.

APRT with elevated doses (≥ 30 Gy, 10.9-fold increased CRC risk, and all-cause mortality as assumed in base case), the optimal screening strategy was colonoscopy from age 35 to 60 every 5 years (**Table 8.3**). Age at primary cancer diagnosis did not influence optimal start age or screening interval, although it did affect optimal stop age. For primary cancer diagnoses at ages 5 or 20 years, optimal stop ages were 55 and 70, respectively.

The optimal screening strategy remained the same as the base case for most alternative assumptions concerning CRC risk and other-cause mortality (**Table 8.3**). Assuming a higher all-cause mortality for all CCS combined and CCS treated with APRT (when based on CCSS data), the age to stop screening was reduced to age 55 years. Screening with colonoscopy every 10 years from age 45 to 65 years was optimal in CCS not treated with APRT when we assumed a lower all-cause mortality or a different mechanism for the increased CRC risk (higher adenoma onset and faster adenoma progression). Assuming higher health-care expenses unrelated to CRC, the optimal starting age for all CCS and those treated with APRT shifted 5 years later to age 45 and 40, respectively. Among the screening strategies included in our PSA, the optimal screening strategy for all CCS combined was robust to model parameter uncertainty. The optimal strategy from the base case remained optimal in almost 90% of replicated scenarios (CEAF=89.4%, at willingness-to-pay threshold of $100,000 per LYG; **Figure 8.2A**). Among CCS with APRT exposure, optimal screening was relatively sensitive to parameter uncertainty. Screening every 10 years from age 35 to 65 (model recommended strategy) remained optimal in 48.1% of the PSA scenarios (**Figure 8.2B**), whereas colonoscopy from age 35 to 55 years every 10 years was optimal in 34.3%. Repeating screening every 10 years from age 30 to 60 years was cost-effective in only 17.6%. Results were sensitive also in CCS not previously treated with APRT: colonoscopy every 10 years during 45-55 and 40-60 years were optimal in 56.6% and 33.6% of PSA replications, respectively (**Figure 8.2C**).

DISCUSSION

This study provides, to our knowledge, the first evidence that the early initiation of colonoscopy screening among CCS is cost-effective and supplies the first quantitative basis for personalizing screening recommendations based on initial diagnosis and APRT dose.

Colonoscopy every 10 years starting at age 35 and 45 years was predicted to produce substantial improvements in LYG and CRC mortality, respectively, among CCS treated and not treated with APRT at an acceptable cost (ICER of, respectively, $92,000 and $57,000 per LYG). Our cost-effectiveness analysis also shows that, among WT survivors, the CCS with the highest risk of developing CRC, colonoscopy screening starting at age 35 years and repeated every 3 years may be appropriate.

Table 8.2. Efficient and currently recommended colonoscopy screening strategies among Childhood Cancer Survivors (CCS) with primary cancer diagnosis at age 15 years.

Screening strategies	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted) *								
	CRC deaths predicted†	CRC mortality†		LYG‡	NNS‖	COLs†	Screening rounds	Total Costs ($1,000¶)	ICER ($1,000¶)
		Reduction, %‡	Δ versus USPSTF§, %						
All CCS									
No screening	37.06	0.00	-73.21	-	-	95.22	0	2821.96	-
COL 50-55 y, 10 y	12.57	66.1	-7.14	57.54	90.94	2227.05	1	3213.66	6.81
COL 50-75 y, 10 y (USPSTF§)	9.93	73.2	-	61.45	107.67	2921.06	3	3475.59	Dominated
COL 45-55 y, 10 y	9.25	75.0	1.82	70.92	113.89	3167.41	2	3687.14	35.38
COL 40-60 y, 10 y (Optimal)#	7.70	79.2	6	79.01	133.70	3925.35	3	4228.77	67.00
COL 35-65 y, 10 y	7.10	80.8	7.63	82.77	153.33	4593.74	4	4861.52	167.94
COL 35-60 y, 5 y	6.53	82.4	9.18	86.97	192.52	5877.77	6	5856.35	237.04
COL 35-65 y, 5 y	6.20	83.3	10.06	87.37	198.18	6115.88	7	5954.34	246.17
COL 35-60 y, 3 y	4.46	88.0	14.77	94.21	279.25	9103.56	9	7951.45	291.86
COL 35-65 y, 3 y	4.00	89.2	16	94.81	290.93	9618.10	11	8175.32	372.07
COL 30-65 y, 3 y	4.11	88.9	15.7	98.34	334.01	11005.72	12	10017.09	521.97
COL 30-70 y, 3 y	3.88	89.5	16.31	98.59	343.04	11382.16	14	10168.58	617.05
COL 25-70 y, 3 y	3.55	90.4	17.21	100.87	391.99	13135.47	16	12525.52	1034.32
COL 25-75 y, 3 y	3.51	90.5	17.31	100.90	394.94	13250.27	17	12566.07	1367.87
CCS treated with APRT									
No screening	63.88	0.0	-72.72	-	-	157.74	0	4980.73	-
COL 50-55 y, 10 y	19.84	68.9	-3.78	108.46	59.77	2632.19	1	4881.48	-0.92
COL 50-75 y, 10 y (USPSTF§)	17.43	72.7	-	112.04	68.19	3167.25	3	5074.20	Dominated
COL 45-55 y, 10 y	14.69	77.0	4.28	133.53	73.31	3606.17	2	5213.47	13.24
COL 40-55 y, 10 y	13.99	78.1	5.38	146.98	80.82	4032.13	2	5557.05	25.55
COL 40-60 y, 10 y	12.25	80.8	8.1	149.70	85.26	4401.75	3	5692.82	49.89

Table 8.2. Efficient and currently recommended colonoscopy screening strategies among Childhood Cancer Survivors (CCS) with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategies	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted) *								
	CRC deaths predicted†	CRC mortality†		LYG‡	NNS‖	COLs†	Screening rounds	Total Costs ($1,000¶)	ICER ($1,000¶)
		Reduction, %‡	Δ versus USPSTF§, %						
COL 35-55 y, 10 y	12.06	81.1	8.4	157.08	93.79	4860.37	3	6226.70	72.39
COL 35-65 y, 10 y (Optimal)#	11.30	82.3	9.59	158.02	96.78	5088.73	4	6313.29	92.14
COL 30-60 y, 10 y	11.04	82.7	10	163.33	105.50	5574.53	4	6981.17	125.73
COL 30-70 y, 10 y	10.73	83.2	10.49	163.62	107.47	5711.78	5	7032.62	176.32
COL 30-75 y, 5 y (COG$)	9.69	84.8	12.11	169.76	137.93	7474.49	10	8405.05	Dominated
COL 35-55 y, 3 y	8.36	86.9	14.19	172.84	156.63	8696.30	7	8729.36	184.17
COL 35-60 y, 3 y	7.51	88.3	15.53	174.28	164.65	9281.40	9	9009.83	193.77
COL 30-60 y, 3 y	7.21	88.7	15.99	181.77	192.22	10893.21	11	10899.11	252.48
COL 30-65 y, 3 y	7.02	89.0	16.29	182.01	194.97	11086.20	12	10983.16	345.04
COL 25-65 y, 3 y	6.48	89.9	17.13	186.14	223.88	12850.47	14	13323.50	566.21
COL 25-70 y, 3 y	6.32	90.1	17.38	186.30	227.74	13108.47	16	13424.69	650.5
COL 25-75 y, 3 y	6.30	90.1	17.42	186.32	229.10	13191.37	17	13454.12	1467.2
CCS not treated with APRT									
No screening	24.68	0.0	-72.91	-	-	64.68	0	1860.17	-
COL 50-55 y, 10 y	9.35	62.1	-10.8	35.46	126.66	1941.75	1	2436.16	16.24
COL 50-75 y, 10 y (USPSTF§)	6.69	72.9	-	39.42	152.54	2744.14	3	2748.27	Dominated
COL 45-55 y, 10 y (Optimal)#	6.74	72.7	-0.24	44.61	160.19	2873.73	2	2961.78	57.48
COL 40-60 y, 10 y	5.54	77.6	4.64	49.69	189.58	3628.54	3	3526.29	111.00
COL 40-70 y, 10 y	5.11	79.3	6.39	50.09	196.93	3853.92	4	3611.11	213.10
COL 35-65 y, 10 y	5.02	79.6	6.73	52.21	218.77	4300.97	4	4163.27	261.27
COL 40-65 y, 5 y	4.49	81.8	8.89	53.12	251.06	5068.92	6	4415.31	275.64

Table 8.2. Efficient and currently recommended colonoscopy screening strategies among Childhood Cancer Survivors (CCS) with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategies	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted) *								
	CRC deaths predicted†	CRC mortality†		LYG‡	NNS‖	COLs†	Screening rounds	Total Costs ($1,000¶)	ICER ($1,000¶)
		Reduction, %‡	Δ versus USPSTF§, %						
COL 35-65 y, 5 y	4.19	83.0	10.1	56.20	293.29	6009.52	7	5399.78	319.63
COL 35-65 y, 3 y	2.66	89.2	16.32	61.27	433.39	9543.18	11	7721.08	458.00
COL 35-70 y, 3 y	2.55	89.7	16.76	61.38	441.29	9765.71	12	7809.57	792.70
COL 30-70 y, 3 y	2.50	89.9	16.95	63.77	512.39	11364.74	14	9754.06	813.27
COL 30-75 y, 3 y	2.43	90.2	17.25	63.82	522.62	11628.33	16	9847.12	1727.38
COL 25-75 y, 3 y	2.27	90.8	17.88	65.03	591.86	13263.67	17	12174.87	1923.92

* Full participation in post-colonoscopy surveillance was assumed; we defined low-risk adenomas (LRA) and high-risk adenomas (HRA) patients considering adenoma size (LRA: 1-2 adenomas ≤ 10mm; HRA: > 2 adenomas ≤ 10mm or 1 adenoma > 10mm); For HRA and LRA individuals, colonoscopy surveillance was simulated with 3- to 5-year intervals according the U.S. Multi-Society Task Force guidelines. Although high-risk pathologies are strongly correlated with size, approximately 3% of adenomas <10mm in diameter may harbor these features.[271]. CRC= colorectal cancer; CCS= childhood cancer survivors; USPSTF = US Preventive Services Task Force; LYG= life years gained; NNS = number needed to screen; COL = colonoscopies; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); COG = Children's Oncology Group;† CRC deaths and number of colonoscopies were not discounted;‡ Compared with no screening; §USTPF guideline for average risk screening; COG guideline for screening of survivors with abdominal or pelvic radiation;‖ NNS indicates the number of screening colonoscopies needed to prevent one colorectal cancer death; ¶ Costs and ICERs in US dollars; # Optimal screening strategy defined as the strategy with highest LYG from screening among those efficient strategies with ICER below $100k/LYG.

Recent studies have shown that CCS develop CRC more frequently and at a younger age than the general population,[9, 10, 12] with the magnitude of the risk comparable to those with family history of CRC (two or more first-degree relatives with CRC).[272] It is not surprising therefore that our results indicate to start screening at age 40 years for all CCS combined (recommended starting age for individuals with family history of CRC).[53] APRT is associated with a substantial increase in CRC risk[10] and, therefore, CCS previously treated with APRT appear to additionally benefit from an even earlier introduction of screening from age 35 years. Despite their lower risk, early screening initiation at age 45 years was cost-effective and optimal among CCS not treated with APRT. Whether this start age should be considered "early" is controversial.[70] Recently updated screening guidelines from the American Cancer Society recommend that individuals at average risk of CRC start regular screening at age 45 years, whereas the USPSTF recommends starting at age 50 years.[266, 273] Our results suggest that CCS treated without APRT should start screening at the earlier age. The optimal screening frequency varied depending on past clinical circumstances. Overall, among survivors treated with APRT, screening was ideally repeated every 10 years, whereas colonoscopy repeated every 3 years was optimal in WT survivors. Shorter intervals are unlikely to be beneficial for other subgroups. The recommendations for high-risk subgroups in our study, such as WT survivors, were based on limited data. These patients merit further study, because WT is relatively common among childhood cancer diagnoses and WT survivors treated with APRT are at high risk of CRC.[10] An epidemiologic evaluation of WT survivors undergoing screening might clarify whether CRC or high-risk polyps arise among those undergoing screening at more infrequent (every 5-10 year) intervals.

This study should be interpreted with caution considering the following limitations. First, our model assumptions regarding all-cause mortality in CCS were based on SEER data (1973-2013), which has very limited follow-up beyond 45 years after initial cancer diagnosis. Sensitivity analyses using different data sources [263, 274] indicated that optimal stopping ages are sensitive to the source used. As prudently recommended for individuals with cystic fibrosis,[51] we would suggest to decide the optimal cessation age of screening considering individual life expectancy (screening should not be indicated in CCS with a life expectancy less than 10-years). Second, the biology underpinning the causes of the higher risk is still unclear. We assumed that the higher risk of CRC shown in CCS was caused by an increased incidence of adenomas,[13] while faster progression from adenoma to CRC may also play a role, as suggested by our model validation in HL survivors.[9] However, our results were not sensitive to this assumption. Third, we assumed full adherence to screening, diagnostic, and surveillance test, because this provides unbiased estimates for optimal screening strategies. However, high-risk CCS may not attend screening as recommended,[275] and therefore, population impact of screening will be lower than our estimates. Still, our results provide useful insight into the potential benefits of CRC screening among CCS. Fourth, we simulated only colonoscopy screening with data from the general population.[77, 251-253] Colonoscopy

Table 8.3. Optimal colonoscopy screening strategies in specific parameter uncertainty analyses and patient subgroups.

Base-case analysis:	**Optimal Screening Strategy**		
	CCS all combined	**CCS treated with APRT**	**CCS not treated with APRT**
	Age 40-60, every 10 years	**Age 35-65, every 10 years**	**Age 45-55, every 10 years**
Specific CCS subpopulation analyses*			
a. Hodgkin Lymphoma survivors	Unchanged	-	-
b. Wilms tumor survivors (primary malignancy at age 5 years)	Age 35-60, every 3 years	-	-
c. CCS treated with APRT at high doses (≥ 30 Gy) and all-cause mortality as in base-case analysis	-	Age 35-60, every 5 years	-
d. CCS treated with APRT at high doses (≥ 30 Gy) and up to 2.6-fold increased all-cause mortality†	-	Age 35-55, every 10 years	-
e. CCS with primary malignancy at age 5 years	Age 40-55, every 10 years	Age 35-55, every 10 years	Unchanged
f. CCS with primary malignancy at age 20 years	Age 40-70, every 10 years	Unchanged	Age 45-65, every 10 years
Parameter uncertainty analyses*			
i. 1.37-fold lower CRC survival‡	Unchanged	Unchanged	Unchanged
ii. CRC risk due to a combination of higher adenoma onset and faster adenoma progression	Unchanged	Unchanged	Age 45-65, every 10 years
iii. Lower all-cause mortality in older ages (≥65 years)	Unchanged	Unchanged	Age 45-65, every 10 years
iv. Higher all-cause mortality according to Mertens, et al., 2008 [268] §	Age 40-55, every 10 years	Age 35-55, every 10 years	Unchanged
v. Higher-than-average health care expenses for conditions unrelated to CRC‖	Age 45-55, every 10 years	Age 40-60, every 10 years	Unchanged

* When age at primary cancer diagnosis was not mentioned, results were estimated assuming first cancer malignancy occurring at age 15 years. CCS = Childhood cancer survivors; APRT = abdominal-pelvic radiation therapy; CRC = colorectal cancer.

† Compared to age-specific other-cause mortality assumed in the base case analysis for CCS, more details are reported in the **Supplementary Methods** (personal information provided by Armstrong, et al, 2016);[15]

‡ In CCS diagnosed with CRC at regional or distant stage; § For CCS treated with APRT, age-specific other cause mortality was assumed up to 1.6-fold increase compared to other cause mortality assumed for CCS all combined [15, 26] ; ‖ Higher hospitalization costs due to the higher probability of being hospitalized seen in CCS compared to US general population (**Supplementary Methods**);[27]

is the preferred screening option in other populations at high risk of CRC, and available literature does not suggest a higher rate of colonoscopy complications in CCS.[9] Fecal immunochemical tests or fecal occult blood testing may be valid alternatives, although their diagnostic performances are still to be established in CCS. Despite its limitations, this study has important clinical implications. Starting colonoscopy screening from age 30 years, as recently recommended by the COG,[144] is unlikely to be the most cost-effective strategy for screening CCS treated with APRT. Our findings suggest that under most clinically plausible scenarios, commencing screening at age 35 years would be the most cost-effective approach, supporting indirectly COG's previous colonoscopy screening recommendations.[261] CCS not previously treated with APRT may also benefit from prompt introduction of colonoscopy screening at age 45 years. Future empirical research should further elucidate which patients have particularly high risk for CRC, such as potentially those treated with alkylating agent chemotherapy or CCS with family history of CRC.[12, 13, 276, 277]

In conclusion, this study shows that under a range of plausible clinical scenarios, early initiation of CRC screening is cost-effective and will prevent most of the CRC deaths expected among CCS. These findings mark an important contribution to the current debate by clinicians, researchers, and policy makers about the appropriateness and necessity of an early CRC screening among these cancer survivors.

SUPPLEMENTARY METHODS

CRC screening costs

Cost-effectiveness analyses were carried out from a modified societal perspective, including patient time costs, but excluding other indirect costs for traveling and time of work. Costs of screening, complications, and life years (LYs) with CRC care are reported in Table 8.1. Our assumptions were based on 2014 Medicare payment rates (including co-payments) for costs of screening; on a cost analysis study of cases hospitalized after endoscopy for colonoscopy complications;[254] and on SEER-Medicare linked data analysis (including co-payments) for LYs with CRC care.[208] Patient time costs were included and all costs were adjusted to 2015 using the annual average Consumer Price Indexes provided by US Bureau of Labor Statistics.[243] However, CCS were seen to have 3.3-fold higher probability to be hospitalized compare to the US general population.[269] For this reason, we carried out a specific one-way sensitivity analysis testing additional hospitalization costs in CCS. We assumed an additional hospitalization cost of $33,900 for each life-year gained by screening in our analysis. We computed this cost considering the annual Medicare per-enrollee spending observed in 2012 for an individual aged 18-48 ($10,300)[278] and the higher probability to be hospitalized observed for CCS compared to the US general population (3.3 x $10,300 = $33,900).[269]

Separate analyses

We performed separate analyses to account for differences in CCS late mortality and to account different CRC risks. Thus, we developed additional version of the model assuming different ages at first cancer diagnosis and for specific groups of CCS. For each additional model version, we performed a cost-effectiveness analysis simulating benefits and costs (10 Million of CCS) of screening in CCS with no screening or under 90 different colonoscopy screening strategies varying in age to start (25, 30, 35, 40, 45, 50 years), interval (every 3, 5, or 10 years), and age to end (55, 60, 65, 70, 75 years).

Different age at first cancer diagnosis

Data from SEER (1973-2013) program shows that – compared with the US general population – CCS have a higher all-cause mortality varying according to age at primary cancer diagnosis (Supplementary Table 8.1). Thus, in our study we assumed that first cancer diagnosis occurred at age 15 years. However, to account for a potential impact of differences in survival we developed two additional versions of the model assuming that first cancer diagnosis occurred, respectively, at age 5 and 20 years. These models were adjusted to reflect CRC and other-cause mortality risk accordingly as described in our study. Parameters of the model were calibrated to replicate the 4.2-fold higher CRC risk observed in the CCS study,[3] assuming that the higher CRC risk in CCS was caused by a more frequent adenoma

onset and started to occur immediately after primary cancer diagnosis. All-cause mortality of CCS was informed by SEER program data.

In addition, we stratified also these analyses to take in account differences in CRC risk due to primary cancer abdominopelvic irradiation, without assuming for those treated a potential impact of RT on all-cause mortality (Same as in the basecase analysis).

Specific groups of CCS

Some Childhood Cancer Survivors (CCS) were treated with localized radiation according to type and localization of primary cancer diagnosis: CCS following a Hodgkin Lymphoma (HL) diagnosis often were treated with chest radiation; and those with Wilms Tumour (WT) often were treated with abdominal radiation.[263] Thus, in addition to the previous adaptions, we adjusted the existing MISCAN-Colon model for the US general population also to reflect CRC and other-cause mortality risk in HL and WT survivors. For HL survivors, we assumed that all individuals were diagnosed with HL at age 15 years considering that HL often occurs in adolescents 15 to 19 years of age.[92] Parameters of the model were adjusted to replicate the cumulative all-cause mortality (since diagnosis date, Supplementary Figure 8.2) and the 5.7-fold higher CRC risk observed in CCS Study.[10, 263] We assumed that increased CRC risk was caused by a combination of shorter adenoma dwell time (50% reduced) and higher adenoma incidence (3-fold increased risk calibrated to replicate the increased CRC incidence as seen among these patients), because with this assumption simulated adenoma detection rates for HL survivors matched best with those reported in an observational study of HL undergoing colonoscopy screening (Supplementary Figure 8.4B).[9] The model was also adjusted to reflect higher CRC-related mortality as seen in a population-based study assessing long-term survival among HL patients with gastrointestinal cancer (1.4-fold after a diagnosis of CRC at distant or regional stage, compared to no-CCS individuals diagnosed with CRC in US in same age and calendar period).[267] For WT survivors, we assumed that in our model WT was diagnosed at age 5 considering that WT is uncommon after age 6 years.[116] Moreover, we adjusted the model to reflect all-cause mortality (since diagnosis date, Supplementary Figure 8.2) and CRC risk (15.5-fold increased) as seen in CCSS for WT survivors.[10, 263] Assumptions on CRC death-specific risk (1.4-fold increased after a diagnosis of CRC at distant or regional stage) and CRC risk composition (adenoma dwell time 50% reduced in combination with a 8-fold more frequent adenoma onset) were based on considerations made for the HL model version, as specific information for the WT survivors are not available. Results are reported in Supplementary Table 8.6.

All-cause mortality in CCS treated with abdominal radiation therapy

To assess a potential effect of different all-cause mortality in CCS treated with abdominal RT we contacted two different research groups (Childhood Cancer Survivors Study, CCSS, Group and Pediatric Oncology Group of Ontario, POGO) and we ask them specific data

on all-cause mortality in CCS not treated (A) and treated, respectively, with abdominal or spinal RT with <30 (B) and ≥ 30 Gy (C). Both kindly responded to our request and sent us all-cause mortality rates (numbers of deaths for all causes and persons-year) for these three CCS groups per year since first cancer diagnosis. As the data information was not sufficient to fully adjust our model to reflect age-specific all-cause mortality for CCS (as we did in our base case analysis), we computed mortality rates ratios comparing

CCS treated with RT (B+C) and all CCS (A+B+C)
and CCS treated with high dosage of RT (C) and all CCS (A+B+C)

to assess the potential impact of abdominal or spinal RT on all-cause mortality in CCS expose to RT compared to what we used in our base case analysis (all-cause mortality in CCS informed using SEER data, no stratification for treatment). Because data was limited and not stratified for age at primary cancer diagnosis when we computed mortality rate ratios we did not stratified estimation for age of first cancer diagnosis. According to our computations (Supplementary Figure 8.3), all-cause mortality was up to 1.5-fold and up to 2.5-fold higher in CCS treated, respectively, with RT (B+C) and with high dosage RT (≥ 30 Gy, C) compared to that observed in average CCS population (A+B+C) in CCSS data. All-cause mortality was up to 1.1-fold and up to 1.2-fold higher in CCS treated, respectively, with RT (B+C) and with high dosage RT (≥ 30 Gy, C) compared to that observed in average CCS population (A+B+C) in POGO data. Considering this information, we adjusted all-cause mortality assumptions in our models as shown in Supplementary Table 8.2. Sensitivity analyses showed that model results informed with POGO data were not sensitive to this assumption and were not reported.

Supplementary Table 8.1. Relative Risks of all-cause death used in base-case analysis and one-way sensitivity analyses.

	First cancer diagnosis at age 15 years							
	Basecase*			Lower all-cause mortality in older CCS			Higher all-cause mortality (Mertens et al, 2008)[268]	
Age groups	No. deaths	RR in SEER	RR assumed in MISCAN†	No. deaths	RR in SEER	RR assumed in MISCAN	RR in SEER	RR assumed in MISCAN†
0-4	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-
10-14	-	-	-	-	-	-	-	-
15-19	-	-	-	-	-	-	-	-
20-24	1,490	22.13	-	1,490	22.13	22.13	20.7	20.7
25-34	556	5.62	5.62	556	5.62	5.62	7.2	7.2
35-39	200	4.63	4.63	200	4.63	4.63	4.7	4.7
40-44	171	4.02	4.02	171	4.02	4.02	5.0	5.0
45-49	146	3.92	3.92	146	3.92	3.92	6.9	6.9
50-54	75	3.22	3.22	75	3.22	3.22	-	6.9
55-59	19	3.43	3.43	19	3.43	3.43	-	6.9
60-64	N/A	-	3.43	N/A	-	3.43	-	6.9
65-69	N/A	-	3.43	N/A	-	3.17‡	-	6.9
70-74	N/A	-	3.43	N/A	-	2.90‡	-	6.9
75-79	N/A	-	3.43	N/A	-	2.64‡	-	6.9
80-84	N/A	-	3.43	N/A	-	2.37‡	-	6.9
85-89	N/A	-	3.43	N/A	-	2.11‡	-	6.9
90-94	N/A	-	3.43	N/A	-	2.11	-	6.9
95-99	N/A	-	3.43	N/A	-	2.11	-	6.9
100	N/A	-	3.43	N/A	-	2.11	-	6.9

* Data from SEER 1973-2013 database (5-years age groups, compared to the US general population) were used as input for MISCAN-Colon model for model version. Assuming a different age at primary cancer diagnosis we informed the model with the following RR observed in SEER data: with primary cancer at age 5 years, ages 25-34 (RR = 4.27), 35-39 (RR = 5.24), 40-44 (RR = 6.02), and 45-100 (RR = 6.02); and with primary cancer at age 20 years, ages 25-34 (RR = 15.49), 35-39 (RR = 4.49), 40-44 (RR = 3.44), 45-49 (RR = 2.86), 50-54 (RR = 2.63), 55-59 (RR = 2.64), and 60-100 (RR = 2.11). No. = number; RR = Relative risk of death; N/A = No deaths were reported for the corresponding age group. SEER = Surveillance, Epidemiology, and End Results; MISCAN = Microsimulation Screening Analysis.

† Relative Risk assumed in MISCAN. RRs after age 60 years were assumed equals to the last observed value (RR at age 55-59) in which the estimate was made with at least 10 events (in basecase and lower all-cause mortality sensitivity analyses); RRs after 35 years since first cancer diagnosis were assumed equals to the last observed value (RR = 6.9) in the higher all-cause mortality sensitivity analysis;‡ In sensitivity analysis of lower all-cause mortality, relative risk assumed a linear decrease from 3.43 (last observed value in which the estimate was made with at least 10 events; CCS with primary cancer diagnosed at age 15) and 2.11 (last lower observed value in CCS in which the estimate was made with at least 10 events; CCS with primary cancer diagnosed at age 20).

Supplementary Table 8.2. Relative Risks of non-colorectal cancer death used in MISCAN-Colon sensitivity analyses

Age groups	First cancer diagnosis occurred at age 15 years:					
	CCS treated with APRT All-cause mortality:			CCS treated with APRT (> 30Gy) All-cause mortality:		
	RR assumed in MISCAN-Colon[*, †, ‡] (basecase analysis)	RR assumed in MISCAN-Colon[‡,§] (CCSS)	RR assumed in MISCAN-Colon[‡,‖] (POGO)	RR assumed in MISCAN-Colon[*, †, ‡] (basecase analysis)	RR assumed in MISCAN-Colon[‡,§] (CCSS)	RR assumed in MISCAN-Colon[‡,‖] (POGO)
25-34	5.62	8.09	3.85	5.62	11.67	3.85
35-39	4.63	7.52	5.67	4.63	10.75	5.67
40-44	4.02	6.51	4.77	4.02	9.88	4.77
45-49	3.92	6.14	4.65	3.92	8.82	4.65
50-54	3.22	4.76	3.82	3.22	6.97	3.82
55-59	3.43	5.25	4.07	3.43	8.22	4.07
60-64	**3.43**	5.25	4.07	**3.43**	8.22	4.07
65-69	**3.43**	5.25	4.07	**3.43**	8.22	4.07
70-74	**3.43**	5.25	4.07	**3.43**	8.22	4.07
75-79	**3.43**	5.25	4.07	**3.43**	8.22	4.07
80-84	**3.43**	5.25	4.07	**3.43**	8.22	4.07
85-89	**3.43**	5.25	4.07	**3.43**	8.22	4.07
90-94	**3.43**	5.25	4.07	**3.43**	8.22	4.07
95-99	**3.43**	5.25	4.07	**3.43**	8.22	4.07
100	**3.43**	5.25	4.07	**3.43**	8.22	4.07

[*] Relative risks from SEER 1973-2013 (5-years age groups, compared to the US general population) for childhood cancer survivors (CCS) were used as input for MISCAN-Colon model in basecase analyses. RR = Relative risk of death; CCS= Childhood Cancer Survivors; APRT = Abdominal or pelvic radiation therapy; CCSS = Childhood Cancer Survivors Study; and POGO = Pediatric Oncology Group of Ontario.

[†] RRs assumed in the basecase analysis is for all CCS combined (with and without abdominal radiation therapy).

[‡] RRs after age 60 years were assumed equals to the last observed value (RR at age 55-59) in which the estimate was made with at least 10 events.

[§] RRs adjusted according to data from Childhood Cancer Survivors Study (CCSS)[8]. RRs assumed in basecase analysis were adjusted as described in Supplementary Methods.

[‖] RRs adjusted according to data from Pediatric Oncology Group of Ontario. RRs assumed in basecase analysis were adjusted as described in Supplementary Methods.

Supplementary Table 8.3. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors (all combined) with primary cancer diagnosis at age 15 years.

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
No screening	37.06	0.00	0.00	0.00	95.22	2821.96	-
COL 50-55 y							
3 y	9.58	74.2	63.76	135.53	3724.27	3831.98	Dominated
5 y	10.63	71.3	61.15	105.63	2791.86	3464.06	Dominated
10 y	12.57	66.1	57.54	90.94	2227.05	3213.66	Efficient
COL 50-60 y							
3 y	8.46	77.2	65.66	158.34	4528.62	4219.56	Dominated
5 y	9.91	73.3	62.27	115.72	3141.76	3618.39	Dominated
10 y	10.33	72.1	61.08	102.25	2733.22	3405.34	Dominated
COL 50-65 y							
3 y	8.01	78.4	66.27	173.63	5043.90	4443.90	Dominated
5 y	9.58	74.2	62.68	123.02	3380.70	3716.66	Dominated
10 y	10.33	72.1	61.08	102.25	2733.22	3405.34	Dominated
COL 50-70 y							
3 y	7.90	78.7	66.37	179.22	5226.17	4516.08	Dominated
5 y	9.44	74.5	62.81	128.10	3538.17	3775.91	Dominated
10 y	9.93	73.2	61.45	107.67	2921.06	3475.59	Dominated
COL 50-75 y							
3 y	7.82	78.9	66.44	187.00	5468.01	4603.00	Dominated
5 y	9.40	74.6	62.84	131.25	3630.31	3807.18	Dominated
10 y	9.93	73.2	61.45	107.67	2921.06	3475.59	Dominated
COL 45-55 y							
3 y	7.34	80.2	77.25	178.28	5298.49	4817.37	Dominated
5 y	8.72	76.5	72.83	129.97	3683.37	4000.65	Dominated
10 y	9.25	75.0	70.92	113.89	3167.41	3687.14	Efficient
COL 45-60 y							
3 y	6.45	82.6	78.73	196.62	6018.64	5162.66	Dominated
5 y	8.04	78.3	73.89	138.75	4026.42	4153.02	Dominated
10 y	9.25	75.0	70.92	113.89	3167.41	3687.14	Dominated
COL 45-65 y							
3 y	6.21	83.2	79.04	203.60	6281.15	5278.22	Dominated
5 y	7.72	79.2	74.29	145.35	4264.63	4251.18	Dominated
10 y	8.33	77.5	72.07	120.88	3472.99	3805.14	Dominated

Supplementary Table 8.3. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors (all combined) with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
COL 45-70 y							
3 y	5.98	83.9	79.30	214.21	6657.50	5429.66	Dominated
5 y	7.58	79.5	74.42	150.00	4421.99	4310.29	Dominated
10 y	8.33	77.5	72.07	120.88	3472.99	3805.14	Dominated
COL 45-75 y							
3 y	5.92	84.0	79.34	220.65	6871.16	5504.94	Dominated
5 y	7.54	79.7	74.45	152.92	4514.12	4341.53	Dominated
10 y	8.21	77.9	72.16	123.91	3574.66	3840.97	Dominated
COL 40-55 y							
3 y	5.76	84.5	87.34	223.98	7010.51	6137.97	Dominated
5 y	7.67	79.3	81.18	156.40	4596.51	4742.49	Dominated
10 y	9.65	74.0	75.95	125.82	3448.60	4044.37	Dominated
COL 40-60 y							
3 y	5.29	85.7	88.12	232.39	7383.06	6317.52	Dominated
5 y	6.99	81.2	82.26	164.23	4938.49	4894.43	Dominated
10 y	7.70	79.2	79.01	133.70	3925.35	4228.77	Optimal[‖]
COL 40-65 y							
3 y	4.78	87.1	88.82	245.74	7932.46	6562.16	Dominated
5 y	6.66	82.0	82.66	170.28	5176.62	4992.55	Dominated
10 y	7.70	79.2	79.01	133.70	3925.35	4228.77	Dominated
COL 40-70 y							
3 y	4.58	87.6	89.03	254.97	8281.38	6699.45	Dominated
5 y	6.52	82.4	82.79	174.66	5334.01	5051.68	Dominated
10 y	7.31	80.3	79.38	138.22	4112.09	4298.72	Dominated
COL 40-75 y							
3 y	4.55	87.7	89.06	258.22	8394.60	6739.53	Dominated
5 y	6.48	82.5	82.82	177.44	5426.15	5082.90	Dominated
10 y	7.31	80.3	79.38	138.22	4112.09	4298.72	Dominated
COL 35-55 y							
3 y	5.46	85.3	92.50	263.45	8325.17	7572.22	Dominated
5 y	7.20	80.6	85.91	185.39	5535.77	5704.43	Dominated
10 y	8.02	78.4	81.64	147.71	4289.46	4744.03	Dominated
COL 35-60 y							

Supplementary Table 8.3. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors (all combined) with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
3 y	4.46	88.0	94.21	279.25	9103.56	7951.45	Efficient
5 y	6.53	82.4	86.97	192.52	5877.77	5856.35	Efficient
10 y	8.02	78.4	81.64	147.71	4289.46	4744.03	Dominated
COL 35-65 y							
3 y	4.00	89.2	94.81	290.93	9618.10	8175.32	Efficient
5 y	6.20	83.3	87.37	198.18	6115.88	5954.34	Efficient
10 y	7.10	80.8	82.77	153.33	4593.74	4861.52	Efficient
COL 35-70 y							
3 y	3.90	89.5	94.92	295.54	9800.22	8247.44	Dominated
5 y	6.06	83.6	87.49	202.36	6273.21	6013.59	Dominated
10 y	7.10	80.8	82.77	153.33	4593.74	4861.52	Dominated
COL 35-75 y							
3 y	3.81	89.7	94.99	302.02	10042.08	8334.37	Dominated
5 y	6.02	83.8	87.52	205.07	6365.32	6044.84	Dominated
10 y	6.97	81.2	82.86	156.05	4695.42	4897.32	Dominated
COL 30-55 y							
3 y	5.23	85.9	96.56	314.91	10023.70	9556.55	Dominated
5 y	6.97	81.2	89.05	216.25	6506.86	6892.45	Dominated
10 y	9.12	75.4	82.19	162.45	4538.75	5323.96	Dominated
COL 30-60 y							
3 y	4.35	88.3	98.02	328.44	10743.18	9901.52	Dominated
5 y	6.29	83.0	90.11	222.58	6848.71	7044.43	Dominated
10 y	7.18	80.6	85.22	167.80	5013.87	5507.72	Dominated
COL 30-65 y							
3 y	4.11	88.9	98.34	334.01	11005.72	10017.09	Efficient
5 y	5.96	83.9	90.52	227.87	7086.87	7142.41	Dominated
10 y	7.18	80.6	85.22	167.80	5013.87	5507.72	Dominated
COL 30-70 y							
3 y	3.88	89.5	98.59	343.04	11382.16	10168.58	Efficient
5 y	5.82	84.3	90.64	231.89	7244.21	7201.75	Dominated
10 y	6.79	81.7	85.59	171.81	5200.54	5577.46	Dominated
COL 30-75 y							
3 y	3.82	89.7	98.64	348.85	11595.84	10243.86	Dominated

Supplementary Table 8.3. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors (all combined) with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[§])	Efficient strategy
5 y	5.78	84.4	90.67	234.54	7336.34	7233.01	Dominated
10 y	6.79	81.7	85.59	171.81	5200.54	5577.46	Dominated
COL 25-55 y							
3 y	4.81	87.0	99.04	366.90	11832.67	11952.17	Dominated
5 y	6.89	81.4	90.85	248.39	7494.05	8322.85	Dominated
10 y	7.94	78.6	84.21	179.81	5236.00	6137.06	Dominated
COL 25-60 y							
3 y	4.30	88.4	99.89	372.94	12217.54	12136.36	Dominated
5 y	6.19	83.3	91.95	254.02	7841.74	8476.99	Dominated
10 y	7.94	78.6	84.21	179.81	5236.00	6137.06	Dominated
COL 25-65 y							
3 y	3.76	89.9	100.65	383.80	12780.40	12385.90	Dominated
5 y	5.85	84.2	92.37	258.98	8082.73	8576.18	Dominated
10 y	6.98	81.2	85.40	184.36	5545.46	6256.54	Dominated
COL 25-70 y							
3 y	3.55	90.4	100.87	391.99	13135.47	12525.52	Efficient
5 y	5.71	84.6	92.49	262.89	8241.57	8635.86	Dominated
10 y	6.98	81.2	85.40	184.36	5545.46	6256.54	Dominated
COL 25-75 y							
3 y	3.51	90.5	100.90	394.94	13250.27	12566.07	Efficient
5 y	5.66	84.7	92.52	265.43	8334.39	8667.34	Dominated
10 y	6.86	81.5	85.49	187.02	5648.03	6292.79	Dominated

[*]Including deaths from complications of screening; CRC = colorectal cancer; LYG = life years gained compared with no screening; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies.

[†]outcomes not discounted.

[‡]compared with no screening.

[§] currency is US dollars.

[‖] The optimal strategy is defined as the most effective strategy with an incremental cost-effectiveness ratio below the willingness-to-pay threshold of $100,000 per life year gained.

Supplementary Table 8.4. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years.

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
No screening	63.88	0.00	0.00	0.00	157.74	4980.73	-
COL 50-55 y							
3 y	16.24	74.6	116.04	85.14	4055.95	5400.28	Dominated
5 y	17.97	71.9	111.95	67.03	3077.33	5066.82	Dominated
10 y	19.84	68.9	108.46	59.77	2632.19	4881.48	Efficient
COL 50-60 y							
3 y	15.29	76.1	117.66	95.96	4662.61	5687.71	Dominated
5 y	17.35	72.8	112.89	71.77	3339.42	5179.66	Dominated
10 y	17.75	72.2	111.74	65.66	3028.98	5022.28	Dominated
COL 50-65 y							
3 y	14.93	76.6	118.13	102.99	5041.43	5850.96	Dominated
5 y	17.10	73.2	113.20	75.14	3514.95	5251.29	Dominated
10 y	17.75	72.2	111.74	65.66	3028.98	5022.28	Dominated
COL 50-70 y							
3 y	14.84	76.8	118.21	105.51	5173.98	5903.30	Dominated
5 y	16.99	73.4	113.30	77.40	3629.31	5294.31	Dominated
10 y	17.43	72.7	112.04	68.19	3167.25	5074.20	Dominated
COL 50-75 y							
3 y	14.79	76.9	118.25	108.96	5348.64	5966.35	Dominated
5 y	16.96	73.5	113.32	78.77	3695.70	5316.89	Dominated
10 y	17.43	72.7	112.04	68.19	3167.25	5074.20	Dominated
COL 45-55 y							
3 y	12.13	81.0	141.97	108.15	5596.59	6161.08	Dominated
5 y	14.20	77.8	135.34	80.70	4009.14	5450.97	Dominated
10 y	14.69	77.0	133.53	73.31	3606.17	5213.47	Efficient
COL 45-60 y							
3 y	11.38	82.2	143.21	116.86	6135.30	6415.85	Dominated
5 y	13.63	78.7	136.22	84.89	4265.62	5562.83	Dominated
10 y	14.69	77.0	133.53	73.31	3606.17	5213.47	Dominated
COL 45-65 y							
3 y	11.20	82.5	143.46	120.13	6328.32	6499.74	Dominated
5 y	13.37	79.1	136.53	87.91	4440.50	5633.98	Dominated
10 y	13.91	78.2	134.49	76.76	3835.70	5300.15	Dominated

Supplementary Table 8.4. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
COL 45-70 y							
3 y	11.02	82.8	143.65	124.90	6602.22	6609.62	Dominated
5 y	13.26	79.2	136.63	89.98	4554.79	5677.10	Dominated
10 y	13.91	78.2	134.49	76.76	3835.70	5300.15	Dominated
COL 45-75 y							
3 y	10.97	82.8	143.68	127.69	6756.20	6663.92	Dominated
5 y	13.23	79.3	136.65	91.24	4621.17	5699.72	Dominated
10 y	13.82	78.4	134.55	78.10	3909.45	5326.16	Dominated
COL 40-55 y							
3 y	9.32	85.4	161.44	133.71	7295.02	7326.29	Dominated
5 y	12.11	81.0	152.27	95.59	4948.59	6095.93	Dominated
10 y	13.99	78.1	146.98	80.82	4032.13	5557.05	Efficient
COL 40-60 y							
3 y	8.92	86.0	162.09	137.82	7574.39	7458.85	Dominated
5 y	11.55	81.9	153.13	99.45	5204.12	6207.33	Dominated
10 y	12.25	80.8	149.70	85.26	4401.75	5692.82	Efficient
COL 40-65 y							
3 y	8.51	86.7	162.66	144.11	7979.40	7637.33	Dominated
5 y	11.29	82.3	153.45	102.28	5379.05	6278.42	Dominated
10 y	12.25	80.8	149.70	85.26	4401.75	5692.82	Dominated
COL 40-70 y							
3 y	8.35	86.9	162.82	148.26	8232.78	7736.78	Dominated
5 y	11.18	82.5	153.55	104.24	5493.29	6321.41	Dominated
10 y	11.94	81.3	150.00	87.39	4539.16	5744.56	Dominated
COL 40-75 y							
3 y	8.33	87.0	162.84	149.68	8314.48	7765.77	Dominated
5 y	11.15	82.6	153.57	105.44	5559.66	6344.04	Dominated
10 y	11.94	81.3	150.00	87.39	4539.16	5744.56	Dominated
COL 35-55 y							
3 y	8.36	86.9	172.84	156.63	8696.30	8729.36	Efficient
5 y	11.17	82.5	162.11	111.81	5893.53	7008.67	Dominated
10 y	12.06	81.1	157.08	93.79	4860.37	6226.70	Efficient
COL 35-60 y							
3 y	7.51	88.3	174.28	164.65	9281.40	9009.83	Efficient

Supplementary Table 8.4. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
5 y	10.60	83.4	163.00	115.41	6149.09	7119.79	Dominated
10 y	12.06	81.1	157.08	93.79	4860.37	6226.70	Dominated
COL 35-65 y							
3 y	7.14	88.8	174.77	170.24	9659.66	9173.03	Dominated
5 y	10.34	83.8	163.31	118.12	6323.97	7190.88	Dominated
10 y	11.30	82.3	158.02	96.78	5088.73	6313.29	Optimal[‖]
COL 35-70 y							
3 y	7.06	89.0	174.85	172.34	9792.10	9225.19	Dominated
5 y	10.23	84.0	163.41	120.00	6438.26	7233.89	Dominated
10 y	11.30	82.3	158.02	96.78	5088.73	6313.29	Dominated
COL 35-75 y							
3 y	7.00	89.0	174.90	175.23	9966.84	9288.27	Dominated
5 y	10.21	84.0	163.43	121.20	6504.64	7256.50	Dominated
10 y	11.20	82.5	158.08	98.00	5162.44	6339.30	Dominated
COL 30-55 y							
3 y	7.95	87.6	180.53	185.15	10355.25	10644.72	Dominated
5 y	10.65	83.3	168.46	128.94	6863.44	8156.88	Dominated
10 y	12.76	80.0	160.64	101.84	5206.19	6844.78	Dominated
COL 30-60 y							
3 y	7.21	88.7	181.77	192.22	10893.21	10899.11	Efficient
5 y	10.08	84.2	169.33	132.32	7119.02	8268.24	Dominated
10 y	11.04	82.7	163.33	105.50	5574.53	6981.17	Efficient
COL 30-65 y							
3 y	7.02	89.0	182.01	194.97	11086.20	10983.16	Efficient
5 y	9.82	84.6	169.64	134.92	7293.88	8339.52	Dominated
10 y	11.04	82.7	163.33	105.50	5574.53	6981.17	Dominated
COL 30-70 y							
3 y	6.84	89.3	182.20	199.16	11360.08	11092.97	Dominated
5 y	9.72	84.8	169.74	136.78	7408.12	8382.50	Dominated
10 y	10.73	83.2	163.62	107.47	5711.78	7032.62	Efficient
COL 30-75 y							
3 y	6.80	89.4	182.23	201.72	11514.04	11147.25	Dominated
5 y	9.69	84.8	169.76	137.93	7474.49	8405.05	Dominated

Supplementary Table 8.4. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
10 y	10.73	83.2	163.62	107.47	5711.78	7032.62	Dominated
COL 25-55 y							
3 y	7.35	88.5	184.82	214.86	12145.84	13005.11	Dominated
5 y	10.53	83.5	171.49	147.14	7849.78	9566.90	Dominated
10 y	11.78	81.6	162.23	111.30	5798.60	7582.59	Dominated
COL 25-60 y							
3 y	6.93	89.2	185.52	218.35	12434.78	13141.04	Dominated
5 y	9.94	84.4	172.41	150.35	8109.94	9679.54	Dominated
10 y	11.78	81.6	162.23	111.30	5798.60	7582.59	Dominated
COL 25-65 y							
3 y	6.48	89.9	186.14	223.88	12850.47	13323.50	Efficient
5 y	9.67	84.9	172.73	152.87	8287.02	9751.67	Dominated
10 y	10.98	82.8	163.21	114.01	6031.18	7670.16	Dominated
COL 25-70 y							
3 y	6.32	90.1	186.30	227.74	13108.47	13424.69	Efficient
5 y	9.56	85.0	172.83	154.68	8402.39	9795.07	Dominated
10 y	10.98	82.8	163.21	114.01	6031.18	7670.16	Dominated
COL 25-75 y							
3 y	6.30	90.1	186.32	229.10	13191.37	13454.12	Efficient
5 y	9.53	85.1	172.85	155.83	8469.25	9817.82	Dominated
10 y	10.88	83.0	163.27	115.20	6105.59	7696.45	Dominated

[*]Including deaths from complications of screening. CRC = colorectal cancer; LYG = life years gained compared with no screening; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies..

[†]outcomes not discounted.

[‡]compared with no screening;

[$]currency in US dollars

[‖] The optimal strategy is defined as the most effective strategy with an incremental cost-effectiveness ratio below the willingness-to-pay threshold of $100,000 per life year gained.

Supplementary Table 8.5. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors not treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years.

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[§])	Efficient strategy
No screening	24.68	0.00	0.00	0.00	64.68	1860.17	-
COL 50-55 y							
3 y	6.85	72.2	40.66	191.70	3418.08	3094.52	Dominated
5 y	7.46	69.8	39.05	149.97	2582.49	2732.69	Dominated
10 y	9.35	62.1	35.46	126.66	1941.75	2436.16	Efficient
COL 50-60 y							
3 y	5.68	77.0	42.68	229.76	4365.44	3558.25	Dominated
5 y	6.70	72.8	40.23	166.69	2997.10	2918.44	Dominated
10 y	7.13	71.1	39.00	143.45	2517.59	2663.14	Dominated
COL 50-65 y							
3 y	5.19	79.0	43.32	255.90	4987.48	3831.04	Dominated
5 y	6.34	74.3	40.68	179.17	3285.99	3038.32	Dominated
10 y	7.13	71.1	39.00	143.45	2517.59	2663.14	Dominated
COL 50-70 y							
3 y	5.07	79.4	43.44	265.69	5210.11	3919.57	Dominated
5 y	6.19	74.9	40.82	188.14	3478.62	3111.35	Dominated
10 y	6.69	72.9	39.42	152.54	2744.14	2748.27	Dominated
COL 50-75 y							
3 y	4.98	79.8	43.52	279.58	5507.78	4026.95	Dominated
5 y	6.14	75.1	40.85	193.76	3592.27	3150.01	Dominated
10 y	6.69	72.9	39.42	152.54	2744.14	2748.27	Dominated
COL 45-55 y							
3 y	5.33	78.4	49.27	259.48	5020.95	4178.90	Dominated
5 y	6.25	74.7	46.37	188.00	3464.83	3331.40	Dominated
10 y	6.74	72.7	44.61	160.19	2873.73	2961.78	Optimal[‖]
COL 45-60 y							
3 y	4.38	82.2	50.86	289.48	5876.52	4594.57	Dominated
5 y	5.53	77.6	47.50	202.21	3872.23	3515.40	Dominated
10 y	6.74	72.7	44.61	160.19	2873.73	2961.78	Dominated
COL 45-65 y							
3 y	4.12	83.3	51.21	301.24	6193.59	4735.20	Dominated
5 y	5.16	79.1	47.95	213.12	4160.17	3634.83	Dominated
10 y	5.77	76.6	45.83	171.06	3234.78	3103.72	Dominated

Supplementary Table 8.5. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors not treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
COL 45-70 y							
3 y	3.87	84.3	51.49	319.69	6652.83	4920.74	Dominated
5 y	5.01	79.7	48.09	221.29	4352.76	3707.77	Dominated
10 y	5.77	76.6	45.83	171.06	3234.78	3103.72	Dominated
COL 45-75 y							
3 y	3.79	84.6	51.54	331.09	6916.40	5013.84	Dominated
5 y	4.96	79.9	48.13	226.49	4466.43	3746.39	Dominated
10 y	5.63	77.2	45.92	176.35	3359.41	3147.65	Dominated
COL 40-55 y							
3 y	4.23	82.9	55.80	329.92	6746.77	5562.34	Dominated
5 y	5.57	77.4	51.54	228.91	4374.51	4112.41	Dominated
10 y	7.49	69.6	46.56	179.28	3081.74	3306.92	Dominated
COL 40-60 y							
3 y	3.73	84.9	56.64	343.14	7188.77	5778.25	Dominated
5 y	4.86	80.3	52.67	241.22	4781.06	4295.93	Dominated
10 y	5.54	77.6	49.69	189.58	3628.54	3526.29	Efficient
COL 40-65 y							
3 y	3.17	87.1	57.42	364.98	7850.68	6075.02	Dominated
5 y	4.49	81.8	53.12	251.06	5068.92	4415.31	Efficient
10 y	5.54	77.6	49.69	189.58	3628.54	3526.29	Dominated
COL 40-70 y							
3 y	2.96	88.0	57.63	381.08	8277.06	6243.49	Dominated
5 y	4.34	82.4	53.27	258.68	5261.51	4488.23	Dominated
10 y	5.11	79.3	50.09	196.93	3853.92	3611.11	Efficient
COL 40-75 y							
3 y	2.92	88.2	57.66	386.79	8416.64	6292.95	Dominated
5 y	4.29	82.6	53.30	263.62	5375.17	4526.84	Dominated
10 y	5.11	79.3	50.09	196.93	3853.92	3611.11	Dominated
COL 35-55 y							
3 y	4.24	82.8	58.73	391.49	8001.99	6994.78	Dominated
5 y	5.28	78.6	54.62	273.97	5315.07	5096.82	Dominated
10 y	6.00	75.7	50.99	210.99	3941.26	4021.83	Dominated
COL 35-60 y							
3 y	3.16	87.2	60.62	414.58	8921.73	7448.72	Dominated

Supplementary Table 8.5. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors not treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted[*,†]	CRC mortality (reduction, %)[*,‡]	LYG[‡]	NNS[†]	COLs[†]	Total Costs ($1,000[$])	Efficient strategy
5 y	4.56	81.5	55.75	284.38	5721.64	5280.11	Dominated
10 y	6.00	75.7	50.99	210.99	3941.26	4021.83	Dominated
COL 35-65 y							
3 y	2.66	89.2	61.27	433.39	9543.18	7721.08	Efficient
5 y	4.19	83.0	56.20	293.29	6009.52	5399.78	Efficient
10 y	5.02	79.6	52.21	218.77	4300.97	4163.27	Efficient
COL 35-70 y							
3 y	2.55	89.7	61.38	441.29	9765.71	7809.57	Efficient
5 y	4.04	83.6	56.34	300.49	6202.10	5472.63	Dominated
10 y	5.02	79.6	52.21	218.77	4300.97	4163.27	Dominated
COL 35-75 y							
3 y	2.45	90.1	61.46	452.69	10063.38	7917.03	Dominated
5 y	3.99	83.8	56.37	305.26	6315.75	5511.25	Dominated
10 y	4.88	80.2	52.30	223.51	4425.52	4207.20	Dominated
COL 30-55 y							
3 y	3.96	83.9	61.57	469.77	9733.69	9012.36	Dominated
5 y	5.12	79.3	56.67	321.45	6287.63	6297.89	Dominated
10 y	7.16	71.0	50.48	236.08	4136.05	4574.06	Dominated
COL 30-60 y							
3 y	3.02	87.8	63.16	488.85	10588.46	9427.83	Dominated
5 y	4.41	82.2	57.79	330.24	6693.91	6481.45	Dominated
10 y	5.22	78.8	53.57	240.56	4681.22	4793.81	Dominated
COL 30-65 y							
3 y	2.76	88.8	63.49	497.51	10905.44	9568.59	Dominated
5 y	4.04	83.6	58.24	338.27	6981.86	6600.86	Dominated
10 y	5.22	78.8	53.57	240.56	4681.22	4793.81	Dominated
COL 30-70 y							
3 y	2.50	89.9	63.77	512.39	11364.74	9754.06	Efficient
5 y	3.89	84.3	58.38	345.09	7174.38	6673.83	Dominated
10 y	4.79	80.6	53.96	246.68	4906.50	4878.45	Dominated
COL 30-75 y							
3 y	2.43	90.2	63.82	522.62	11628.33	9847.12	Efficient
5 y	3.84	84.4	58.41	349.71	7288.02	6712.46	Dominated
10 y	4.79	80.6	53.96	246.68	4906.50	4878.45	Dominated

Supplementary Table 8.5. Outcomes with colonoscopy screening strategies that vary by screening interval, ages to begin, and end screening among childhood cancer survivors not treated with abdominal or pelvic radiation therapy with primary cancer diagnosis at age 15 years. (*continued*)

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted*,†	CRC mortality (reduction, %)*,‡	LYG‡	NNS†	COLs†	Total Costs ($1,000§)	Efficient strategy
COL 25-55 y							
3 y	3.67	85.1	63.05	550.08	11557.16	11430.23	Dominated
5 y	5.09	79.4	57.71	371.32	7274.10	7738.76	Dominated
10 y	5.96	75.8	52.57	261.39	4893.23	5430.52	Dominated
COL 25-60 y							
3 y	3.14	87.3	63.95	557.65	12011.75	11651.00	Dominated
5 y	4.34	82.4	58.88	377.92	7686.83	7924.41	Dominated
10 y	5.96	75.8	52.57	261.39	4893.23	5430.52	Dominated
COL 25-65 y							
3 y	2.54	89.7	64.77	573.11	12688.60	11953.31	Dominated
5 y	3.97	83.9	59.35	385.22	7977.90	8045.07	Dominated
10 y	4.95	79.9	53.83	266.54	5258.87	5573.89	Dominated
COL 25-70 y							
3 y	2.31	90.6	65.00	586.60	13122.22	12124.70	Dominated
5 y	3.81	84.6	59.49	391.57	8172.15	8118.55	Dominated
10 y	4.95	79.9	53.83	266.54	5258.87	5573.89	Dominated
COL 25-75 y							
3 y	2.27	90.8	65.03	591.86	13263.67	12174.87	Efficient
5 y	3.76	84.8	59.52	396.11	8286.61	8157.45	Dominated
10 y	4.81	80.5	53.93	270.99	5384.52	5618.23	Dominated

*Including deaths from complications of screening; CRC = colorectal cancer; LYG = life years gained compared with no screening; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies.

†outcomes not discounted.

‡compared with no screening;

§currency in US dollars

|| The optimal strategy is defined as the most effective strategy with an incremental cost-effectiveness ratio below the willingness-to-pay threshold of $100,000 per life year gained.

Supplementary Table 8.6. Efficient colonoscopy screening strategies among Hodgkin Lymphoma and Wilms tumor survivors.

Screening strategy	Outcomes per 1,000 CCS free of diagnosed cancer and aged 25 years in 2017 (3% discounted)						
	CRC deaths predicted*,†	CRC mortality (reduction, %)*,†,‡	LYG‡	NNS*,§	COLs*	Total Costs ($1,000‖)	ICER ($1,000‖)
Hodgkin Lymphoma survivors							
No screening	51.49	-	-	-	119.3	3436.11	-
COL 50-55 y, 10 y	16.62	67.7	84.09	69.21	2413.42	3774.59	4.03
COL 45-55 y, 10 y	12.21	76.3	103.85	85.76	3368.84	4227.86	22.94
COL 40-55 y, 10 y	12.27	76.2	112.39	94.87	3720.73	4605.63	44.2
COL 40-60 y, 10 y	10.21	80.2	115.67	100.49	4148.34	4772.1	50.82¶
COL 35-65 y, 10 y	9.38	81.8	121.86	114.48	4820.58	5409.98	103.04
COL 30-70 y, 10 y	8.96	82.6	125.86	127.75	5433.28	6132.17	180.4
COL 35-60 y, 5 y	8.68	83.2	126.97	140.75	6025.68	6341.26	187.77
COL 35-60 y, 3 y	5.89	88.6	137.1	202.93	9253.81	8394.88	202.8
COL 35-65 y, 3 y	5.45	89.4	137.68	210.76	9703.28	8590.96	335.69
COL 30-65 y, 3 y	5.5	89.3	142.93	241.64	11112.96	10432.54	351.02
COL 30-70 y, 3 y	5.27	89.8	143.18	247.51	11439.9	10564.38	529.69
COL 25-70 y, 3 y	4.81	90.7	146.6	282.57	13190.38	12915.14	687.02
COL 25-75 y, 3 y	4.77	90.7	146.63	284.46	13289.84	12950.42	1321.1
Wilms tumor survivors							
No screening	117.99	-	-	-	252.09	8046.87	-
COL 50-55 y, 10 y	42.11	64.3	210.44	35.45	2690.26	7502.28	-2.59
COL 45-55 y, 10 y	31.55	73.3	265.08	43.04	3720.42	7634.04	2.41
COL 40-55 y, 10 y	30.57	74.1	292.87	47.58	4159.58	7889.98	9.21
COL 40-60 y, 10 y	26.57	77.5	299.69	49.92	4563.99	7998.4	15.91
COL 35-55 y, 10 y	26.26	77.7	316.27	54.79	5025.85	8483.39	29.24
COL 35-65 y, 10 y	24.39	79.3	318.77	56.43	5282.22	8565.08	32.75
COL 30-60 y, 10 y	24.12	79.6	330.29	61.45	5768.4	9194.17	54.6
COL 30-70 y, 10 y	23.29	80.3	331.13	62.6	5928.08	9249.58	65.78
COL 35-55 y, 3 y	18.35	84.5	352.27	91.26	9093.53	10714.7	69.29
COL 35 -60 y, 3 y	16.28	86.2	356.03	95.76	9739.89	10987.79	72.68¶
COL 30-60 y, 3 y	15.9	86.5	372.66	111.52	11385.32	12826.84	110.56
COL 30-65 y, 3 y	15.41	86.9	373.36	113.11	11602.85	12913.81	124.5
COL 30-70 y, 3 y	14.94	87.3	373.91	115.66	11918.89	13034.06	221.93
COL 25-65 y, 3 y	14.19	88.0	383.1	129	13389.81	15207.83	236.39
COL 25-70 y, 3 y	13.74	88.4	383.57	131.32	13690.43	15319.64	237.71
COL 25 -75 y, 3 y	13.67	88.4	383.63	132.2	13790.93	15354.38	594.92

*CRC death and number of colonoscopies were not discounted. COL = colonoscopy; CRC = colorectal cancer; Lys = Life-years; LYG = LYs gained compared with no screening; ICER = Incremental cost-effectiveness ratio (ΔCosts/ΔLYs gained compared to the previous less costly efficient strategy).

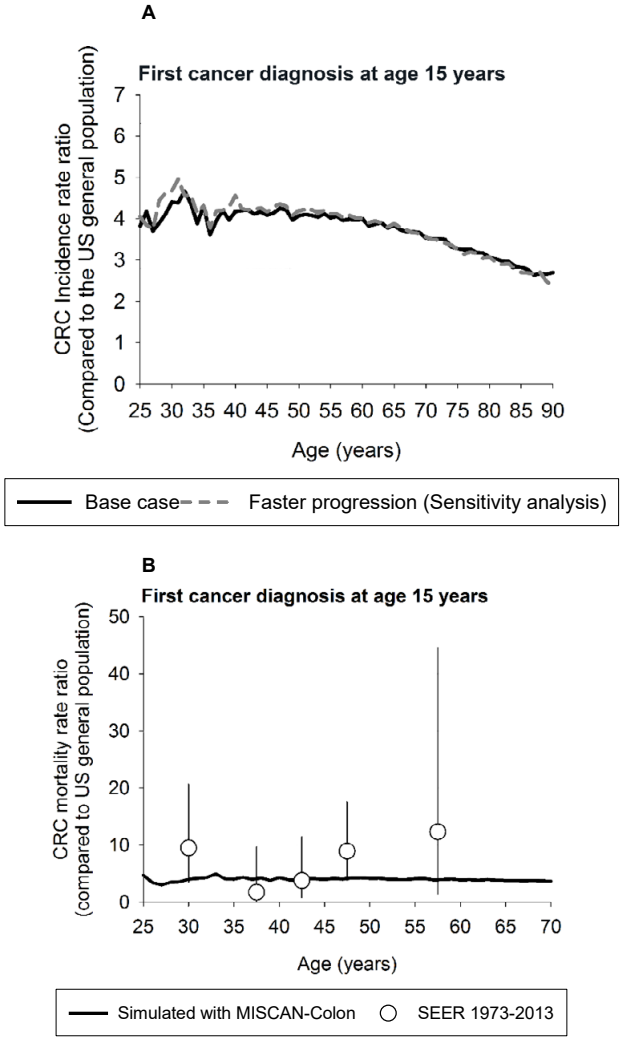
†Including deaths from complications of screening;

‡compared with no screening;

§NNS: number needed to screen to prevent a CRC death defined as the number of screening tests needed to prevent a CRC death;

‖currency in US dollars.

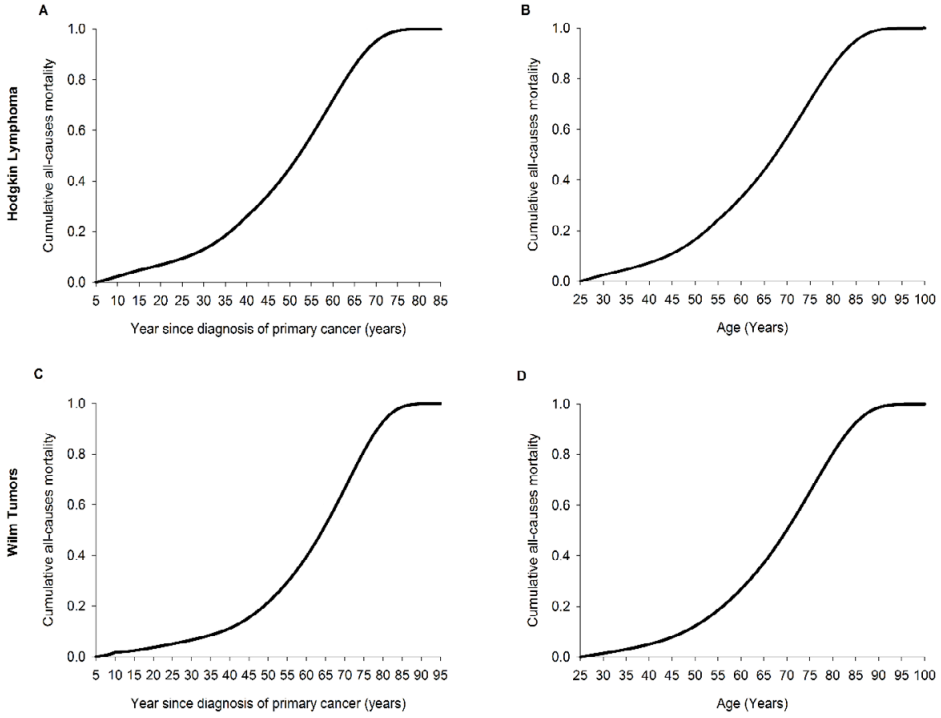
¶ Indicates the optimal strategy, defined as the most effective strategy with an incremental cost-effectiveness ratio below the willingness-to-pay threshold of $100,000 per life year gained.



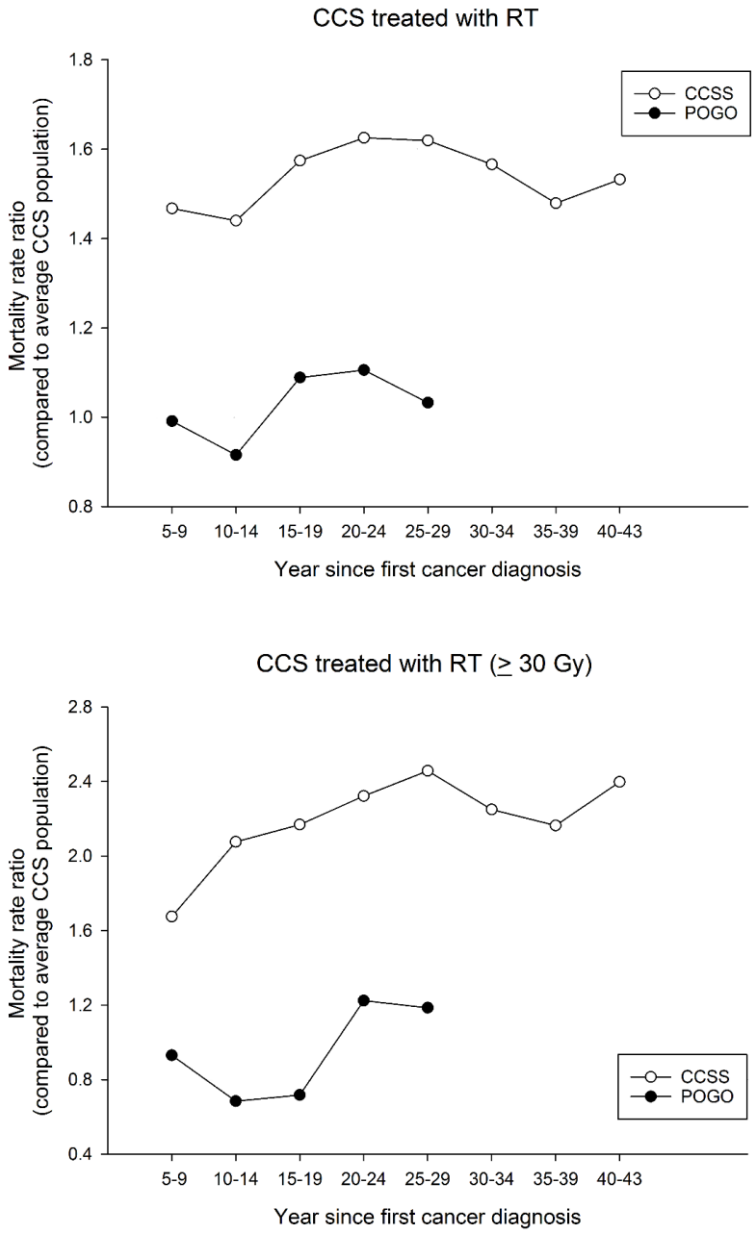
Supplementary Figure 8.1. Age-specific colorectal cancer relative risk (A) and colorectal cancer mortality risk (B) compared with US general population.

(A). Age-specific colorectal (CRC) Relative Risk (Incidence Rate Ratio compare to the US general population, Henderson et al, 2012) under two different assumptions for increased CRC risk: base case (more frequent adenoma onset) and faster adenoma progression (combination of shorter adenoma-to-malignancy progression time and more frequent adenoma onset). Results were simulated using MISCAN-Colon assuming no screening. Horizontal lines indicate increased CRC according to Henderson et al. (solid); and 95% confidence intervals (dash).[10] CRC = colorectal cancer; MISCAN = Microsimulation Screening Analysis; SEER = Surveillance, Epidemiology, and End Results.

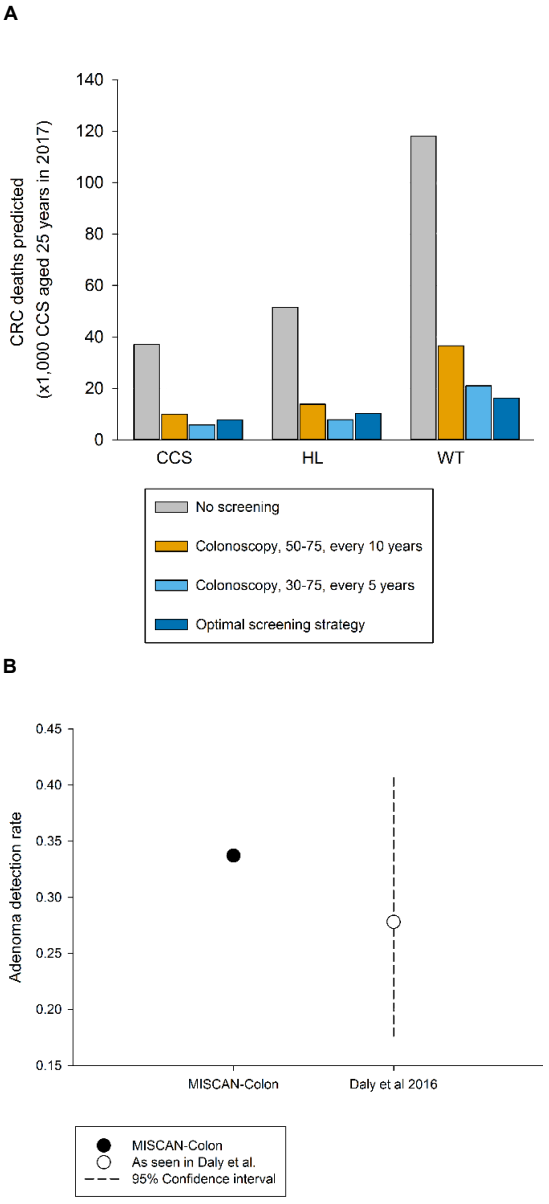
(B). Age-specific Relative Risk of dying for CRC (Mortality Rate Ratio compare to the US general population). Results for CCS and US general population were simulated using MISCAN-Colon assuming no screening. Increased adenoma risk was assumed according to the base case assumption (Henderson et al, 2012).[10] Early deaths for primary CRC were excluded in MISCAN-Colon simulations, whereas those might be included in the SEER data (comparison of RRs in the first 10 years since primary cancer diagnosis may be affected by this limitation).



Supplementary Figure 8.2. Cumulative all-cause mortality by year since primary cancer diagnosis **(A and C)** and by attained age **(B and D)** simulated with Microsimulation Screening Analysis-Colon model (no screening) for Hodgkin Lymphoma **(A and B)** and Wilms Tumors **(C and D)** survivors.[10, 263]



Supplementary Figure 8.3. Mortality rate ratios in childhood cancer survivors treated with radiation therapy compared to the average childhood cancer survivor population by year since first cancer diagnosis.
Risks for the basecase analysis were taken from the Childhood Cancer Survivor Study (CCSS), and sensitivity analyses were performed using population-based data from the Pediatric Oncology Group of Ontario (POGO).
RT = radiation therapy; CCS= childhood cancer survivor; CCSS = childhood cancer survivor study; POGO = Pediatric Oncology group of Ontario.



Supplementary Figure 8.4. Colorectal cancer deaths predicted by the model in an average population of childhood cancer survivors (CCS), Hodgkin Lymphoma survivors (HL), and Wilms Tumour survivors (WT) under four different main colonoscopy screening scenarios.

(A). Bars indicate colorectal cancer deaths predicted by the model in an average population of CCS, in Hodgkin Lymphomas, and Wilms tumour survivors under four different main colonoscopy screening scenarios: no screening, Colonoscopy every 10 years between age 50 and 75 (US Preventive Task Force's general population recommended screening strategy), Colonoscopy every 5 years between age 30 and 75 (the Children's Oncology Group screening indication for CCS treated with APRT), and the corresponding optimal colonoscopy screening strategy suggested by our model (average CCS and Hodgkin Lymphomas: Colonoscopy between age 40 and 60 every 10 years; WT: colonoscopy between age 35 and 60 years every 3 years). CRC = colorectal cancer; CCS = childhood cancer survivor; HL= Hodgkin lymphoma survivors; and WT = Wilms tumour survivors; MISCAN-Colon = Microsimulation Screening Analysis-Colon. **(B).** Adenoma detection rate simulated with and observed in a colonoscopy observational study among Childhood Cancer Survivors (major part of them were Hodgkin Lymphoma survivors)[2]. Results were simulated using MISCAN-Colon assuming for HL survivors an increased CRC risk caused by a combination of more frequent adenoma onset and faster adenoma progression (twice as fast as in the basecase). Comparison between the simulated and observed adenoma detection rate supports the hypothesis of a faster adenoma progression in HL survivors and other CCS at higher risk of developing CRC (WT survivors or CCS treated with APRT at dosage >30Gy) compared to US general population.