Computed Tomographic Colonography to Screen for Colorectal Cancer, Extracolonic Cancer, and Aortic Aneurysm

Model Simulation With Cost-effectiveness Analysis

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Background: In addition to detecting colorectal neoplasia, abdominal computed tomography (CT) with colonography technique (CTC) can also detect unsuspected extracolonic cancers and abdominal aortic aneurysms (AAA). The efficacy and cost-effectiveness of this combined abdominal CT screening strategy are unknown.

Methods: A computerized Markov model was constructed to simulate the occurrence of colorectal neoplasia, extracolonic malignant neoplasm, and AAA in a hypothetical cohort of 100 000 subjects from the United States who were 50 years of age. Simulated screening with CTC, using a 6-mm polyp size threshold for reporting, was compared with a competing model of optical colonoscopy (OC), both without and with abdominal ultrasonography for AAA detection (OC-US strategy).

Results: In the simulated population, CTC was the dominant screening strategy, gaining an additional 1458 and 462 life-years compared with the OC and OC-US strategies and being less costly, with a savings of $266 and $449 per person, respectively. The additional gains for CTC were largely due to a decrease in AAA-related deaths, whereas the modeled benefit from extracolonic cancer downstaging was a relatively minor factor. At sensitivity analysis, OC-US became more cost-effective only when the CTC sensitivity for large polyps dropped to 61% or when broad variations of costs were simulated, such as an increase in CTC cost from $814 to $1300 or a decrease in OC cost from $1100 to $500. With the OC-US approach, suboptimal compliance had a strong negative influence on efficacy and cost-effectiveness. The estimated mortality from CT-induced cancer was less than estimated colonoscopy-related mortality (8 vs 22 deaths), both of which were minor compared with the positive benefit from screening.

Conclusion: When detection of extracolonic findings such as AAA and extracolonic cancer are considered in addition to colorectal neoplasia in our model simulation, CT colonography is a dominant screening strategy (ie, more clinically effective and more cost-effective) over both colonoscopy and colonoscopy with 1-time ultrasonography.

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COMPUTED TOMOGRAPHIC (CT) colonography (CTC) has been shown to be a feasible approach for effective colorectal cancer (CRC) screening.[1,2] Prior cost-effectiveness analyses comparing optical colonoscopy (OC) and CTC have had mixed results but have generally shown OC to be more cost-effective.[3-6] However, when reasonable polyp detection sensitivities for CTC have been assumed, this test has been competitive with colonoscopy and is clearly cost-effective compared with not screening.

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A unique added dimension of CTC screening compared with endoscopy is the ability to evaluate the extracolonic structures of the abdomen and pelvis.[7] Although much attention has been placed on the costs related to additional workup for extracolonic findings found at CTC, the potential benefit in terms of identifying life-threatening conditions, such as extracolonic cancer and abdominal aortic aneurysm (AAA), has not been assessed.[8-11] In fact, a previous cost-effectiveness analysis[12] has shown that 1-time abdominal ultrasonographic (US) screening for AAA can provide high clinical efficacy at a relatively low cost. Without any modification in protocol, CTC can provide for AAA screening that equals or surpasses US evaluation. The impact of screening for extracolonic cancer with noncontrast CTC, as well as the trade-off between the theoretical risk of radiation-induced cancer and colonoscopy-related complications are less clear.[13,14]

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We assessed the potential impact of extracolonic findings on the efficacy and cost-effectiveness of CRC screening with CTC. We also compared CTC with a strategy of colonoscopy combined with 1-time US evaluation (OC-US strategy).

METHODS

BASE CASE ANALYSIS

A Markov model was constructed, and simulation was performed on a hypothetical cohort of 100 000 subjects aged from 50 to 100 years. This model has been previously validated for CRC screening but without consideration for extracolonic findings.[6,15] Baseline assumptions and ranges used in the model are provided in **Table 1**. To assess the impact of extracolonic findings at CTC, we simulated those serious diseases that may be detected by an unenhanced CT scan of the abdomen and pelvis, including ovarian, pancreatic, hepatic, renal, and (lower) bronchogenic malignant neoplasms, as well as AAA. The principal health states of the model are shown in **Figure 1**.

The natural history of colorectal neoplasia was calibrated to reproduce the age- and sex-specific prevalence at autopsy and screening studies of both adenomas and large adenomas,[15-19] and the age- and stage-specific incidence and mortality rate computed by the Surveillance, Epidemiology, and End Results (SEER) program (**Figure 2**).[20] The natural history of AAA was simulated to match the age-specific prevalence rate for male subjects available from large studies.[22,23] The prevalence of AAA in women was assumed to be 10% of the corresponding age-dependent male values.[24] A yearly risk of either a high-mortality–related surgery owing to AAA rupture or a low-risk surgery owing to an opportunistically detected nonruptured AAA in unscreened subjects was estimated on the basis of 3 randomized screening studies for male subjects older than 65 years and calibrated to reproduce the AAA death rate among the general population in the United States reported by the National Vital Statistics Report (Figure 2).[21,25-27] Age- and sex-specific incidence, stage, and stage-related mortality for the extracolonic malignant neoplasms were estimated on the basis of SEER data and validated with the corresponding death rates reported by the National Vital Statistics Report (Figure 2).[21,28] Natural attrition for the general population in the United States was also taken into account.[29]

SCREENING INTERVENTIONS

The health interventions superimposed on the natural history model were CTC (with a 6-mm polyp size reporting threshold), OC without US, and OC with 1-time abdominal US (OC-US strategy). The colorectal screening tests were assumed to be repeated every 10 years until age 80 years, with their efficacy related to the polyp and CRC detection rates listed in Table 1. In the CTC strategy, detection of a lesion 6 mm in size or greater was followed by OC with polypectomy. Further details on our specific CRC screening model are provided elsewhere.[6,15] We also included the additional theoretical risk of cancer induced by each CTC, distributing the lifetime risk of 0.01%, which has been estimated for an optimized protocol at age 50 years.[13] This risk was considered to be halved at age 70 years and further reduced at age 80 years. Detection of AAA in the CTC and OC-US strategies resulted in both a reduction of surgery from AAA rupture and in an increase in surgery for nonruptured AAA, as previously described.[30] In the OC-US strategy, a 1-time US examination at 65 years was simulated, with an assumed high accuracy equal to that of CTC. Efficacy of US was optimistically assumed to last for 15 years after the procedure, even though an increased risk of AAA rupture after 5 to 10 years has been described.[12]

Extracolonic cancer detection in the CTC strategy was assumed to result in a downstaging of the disease compared with those diseases arising in the other strategies, including no screening. Specifically, we assumed that the cancer-specific distribution of stages, as well as related costs and mortality, for extracolonic cancers detected at CTC screening would shift down approximately 50%, but only during the year of screening (ie, a 50% shift from distant to regional and from regional to local).[14,31,32] The distribution of local, regional, and distant disease was assumed to be different for asymptomatic CTC-detected cancers vs incident cancers in the non-CTC groups, which would be more likely to present with symptoms and a more advanced stage (Table 1). The sensitivity values for CT detection of extracolonic cancers were mainly derived from the literature. If data for unenhanced CT were not available, 2 of us (P.P. and A.L.) estimated its accuracy, taking into account the relatively poorer performance of unenhanced CT and the detection rates of extracolonic cancers in historical CTC series (2.7% at 65 years).[7-11] For lung cancer, we assumed a 25% sensitivity because only one-quarter to one-third of the lungs are visualized on a typical CTC study.

COSTS

Medicare reimbursement data for screening and surveillance procedures, for CRC and extracolonic malignant neoplasms according to stage of disease at diagnosis, and for AAA elective or emergency surgery were converted to 2006 US dollars by using the medical component of the consumer price index for that year (Table 1).[33] Previous estimates on the cost of additional workup for extracolonic findings detected at CTC have ranged from $24 to $34 per patient, and the cost was $31 per patient in our own experience.[8-11] We therefore assumed an additional expenditure of $31 for each CTC examination. Indirect costs for CTC, OC, and US were estimated based on a median hourly income rate of $18.62/h.[34,35]

COST-EFFECTIVENESS ANALYSIS

Clinical effectiveness of screening is measured in terms of life-years gained through prevention or downstaging of all the included diseases. In the natural history and screening models, the life-years lost by the age-dependent proportion of patients dying prematurely of CRC, extracolonic malignant neoplasms, or AAA are accumulated for each cycle during the entire expected lifetime. The number of life-years gained as a result of screening corresponds to the difference in life-years lost from cancer- or AAA-related deaths with and without screening by the Markov model, or between 2 different screening strategies. The incremental cost-effectiveness ratio (ICER) between 2 strategies, including the possibility of no screening, was defined as the difference in cost divided by the difference in life expectancy, which represents the cost per life-years gained. Both future costs and future life-years gained were discounted using an annual rate of 3%. An ICER of $100 000 per life-year gained was used as a general threshold to differentiate an efficient procedure from an inefficient procedure.[36]

SENSITIVITY ANALYSIS

Sensitivity analysis was performed by employing 2 different methods. First, the model parameters were varied simultaneously and randomly for 10 000 interactions in a Monte Carlo simu-

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Table 1. Model Characteristics and Parameters Used for the Base Case and Sensitivity Analyses[a]

Variable	Parameter
Model characteristics	
Model type	State transition model (Markov)
Hypothetical population	100 000 50-year-old subjects from the United States
Perspective	Societal
Screening age, range	50-80 y
Time horizon	Lifetime
Intervention	OC (± 1-time US at age 65 y) or CTC every 10 y
Natural history[b]	
Colorectal neoplasia	
Adenoma prevalence at age 50 y, % (range)	15 (10-45)[6,15-19]
<10 mm polyp	95[6,15-19]
≥10 mm polyp,	5[6,15-19]
New adenomatous polyp rate (% per year)[c]	1.9-3.3[41]
Annual transition rate, % (range)	
From ≤5 mm to 6-9 mm[c]	2-4 (0.02-7.8)[6,42]
From 6-9 mm to ≥10 mm[c]	2-4 (0.02-7.8)[6,42]
From ≥10 mm to LOC CRC[c]	3-4 (1-10)[6,43]
From LOC CRC to REG CRC	33 (25-10)[20]
From REG CRC to DIS CRC	40 (20-60)[20]
Advanced ≥10 mm/advanced <10 mm rate, % (range)	90 (70-100)[20]
Polypoid/de novo rate of CRC carcinogenesis, % (range)	85 (70-100)[45]
Annual transition rate to de novo cancer, (range)[c]	0.008-0.16[6]
Symptomatic presentation, % (range)	
Of LOC CRC	20 (5-40)[20]
Of REG CRC	65 (30-80)[20]
Of DIS CRC	100[20]
Annual mortality rate, %/y (range)	
For LOC CRC in the first 5 y	1.7 (0.9-2.5)[28]
For REG CRC in the first 5 y	8.6 (4-12)[28]
Mean survival from DIS CRC, y	1.9[28]
Hyperplastic polyp prevalence at age 50 y, % (range)	10 (5-20)[15-19]
Annual hyperplastic polyp incidence rate, % (range)	5 (2-8)[15-19]
Aortic aneurysm, prevalence	
In males, age, y, % (range)	1.0 (0.5-2)[22,23]
50	3.4 (1.7-6.8)[22,23]
60	5.5 (2.2-8)[22,23]
65	6.1 (3-9)[22,23]
70	
In females	10% of age-specific male prevalence[24]
Annual transition rate from no AAA to AAA, % (range)[d]	0.1-0.2 (0.05-0.4)[21,25-27]
Annual AAA risk for ruptured AAA surgery, unscreened group, % (range)[c]	0.5-1.9 (0.1-3.8)[21,25-27]
Annual AAA risk for nonruptured AAA surgery, unscreened group, % (range)[c]	0.4-1.4 (0.1-2.8)[21,25-27]
Ruptured AAA mortality, % (range)	80 (50-100)[21,25-27]
Nonruptured AAA surgical mortality, % (range)	3.1 (1.5-5)[21,25-27]
Extracolonic cancer, annual incidence, cases/100 000, range[c]	
Of ovarian cancer	24-60[28]
Of renal cancer	18-60[28]
Of pancreatic cancer	10-88[28]
Of liver cancer	10-29[28]
Of lung cancer	50-427[28]
Stage distribution for extracolonic cancer (LOC/REG/DIS)	
Ovarian cancer	25/8/66[28]
Renal cancer	57/21/22[28]
Pancreatic cancer	9/26/52[28]
Liver cancer	40/32/28[28]
Lung cancer	17/27/56[28]
5-y stage-specific mortality for extracolonic cancer (LOC/REG/DIS)	
Ovarian	7/31/70[28]
Renal	10/38/90[28]
Pancreatic	80/92/98[28]
Liver	78/93/97[28]
Lung	50/85/97[28]

(continued)

lation (using Lumenaut statistical software, version 3.4.9; Lumenaut Ltd, Hong Kong). This provided estimates on the variability in cost-effectiveness, expressed as 10% to 90% percentiles, which arises when variables in the model are allowed to take on distributions. Second, a systematic sensitivity analysis was performed, mainly based on the screening parameters for CRC and AAA.

RESULTS

EFFICACY

Without any screening intervention, the simulated cohort of 50-year-old persons will experience a cumulative loss

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Table 1. Model Characteristics and Parameters Used for the Base Case and Sensitivity Analyses[a] (cont)

Variable	Parameter
Screening	
Adherence, % (range)[e]	100 (50-100)
Compliance, % (range)[f]	100 (50-100)
Colorectal neoplasia	
CTC sensitivity, % (range)	
For ≤5 mm polyps	0 (Not reported at CTC)
For 6-9 mm polyps	70 (45-90)[46,47]
For ≥10 mm polyps	85 (35-100)[46,47]
For CRC, %	95 (70-100)[46,47]
CTC specificity, %	86 (35-100)[46,47]
OC sensitivity, % (range)	
For ≤5 mm polyps	80 (50-100)[48,49]
For 6-9 mm polyps	85 (50-100)[48,49]
For ≥10 mm polyps	90 (50-100)[48,49]
For CRC	95 (70-100)[48,49]
OC specificity, % (range)	99 (80-100)[48,49]
OC perforation rate, % (range)	0.06 (0-0.1)[50]
CTC perforation rate, % (range)	0.0005 (0-0.1)[51]
Polypectomy bleeding, % (range)	0.48 (0-1)[50]
Polypectomy perforation, % (range)	0.11 (0-0.3)[50]
OC-related death rate, % (range)	0.006 (0-0.01)[50]
Lifetime risk of CTC radiation-induced cancer, %[c,g]	0.01-0.006 (0-0.2)[13]
Annual AA, risk %[c]	
For ruptured AAA surgery, screened group	0.2-0.8 (0-1.9)[21,25-27,30]
For nonruptured AAA surgery, screened group	1.1-3.9 (0-7)[21,25-27,30]
CTC sensitivity for extracolonic cancer, % (range)	
Ovarian	70 (30-100)[52]
Renal	70 (30-100)[53]
Pancreatic	70 (30-100)[54]
Liver	63 (30-100)[55]
Lung	25 (10-50)
Stage distribution for extracolonic cancer (LOC/REG/DIS)	
Ovarian	64/25/11[14,31,32]
Renal	69/18/12[14,31,32]
Pancreatic	40/31/30[14,31,32]
Liver	58/26/17[14,31,32]
Lung	45/27/28[14,31,32]
Costs, colorectal neoplasia, $ (range)	
OC	877 (400-2000)[4,6,56]
CTC	665 (400-2000)[4,6,56]
OC with polypectomy	1265 (700-2000)[4,6,56]
Radiologic workup for extracolonic findings	31 (10-100)[8-11]
OC bleeding	5494 (2000-9592)[4,6,56]
OC perforation	16 380 (8000-28 600)[4,6,56]
Indirect cost OC[h]	223[35]
Indirect cost CTC[h]	149[35]
LOC CRC treatment	51 800 (25 000-99 502)[4]
REG CRC treatment	76 500 (35 000-150 000)[4]
DIS CRC treatment	80 000 (40 000-160 000)[4]
Costs, aortic aneurysm, $ (range)	
US	91 (50-150)[57]
Indirect cost US[h]	75
Rupture AAA surgery	48 000 (24 000-96 000)[58]
Nonruptured AAA surgery	48 000 (24 000-96 000)[58]
Costs, extracolonic cancer treatment, $ (routine/screening)[i]	
Ovarian	63 927/43 357[14]
Renal	31 613/31 613[14]
Pancreatic	59 967/89 080[14]
Liver	93 640/96 144[14]
Lung	97 565/96 973[14]

Abbreviations: AAA, abdominal aortic aneurysm; CRC, colorectal cancer; CTC, computed tomographic colonography; DIS, distant; LOC, localized; OC, colonoscopy; REG, regional; US, abdominal ultrasonography for AAA detection.

[a] Data are given as percentages except where noted.

[b] Data are given as base case value (range).

[c] Age specific. The first range indicates the age-specific range adopted in the analysis, and the second range indicates the range adopted in the sensitivity analysis.

[d] Sex and age specific. The first range indicates the age-specific range adopted in the analysis, and the second range indicates the range adopted in the sensitivity analysis.

[e] Initial adherence was defined as compliance to the first examination.

[f] Defined as compliance to repeated examinations.

[g] Distributed as follows: 46%, CRC; 35%, kidney cancer; 19%, liver cancer. Data are from Brenner et al.[13]

[h] Indirect costs for the different strategies were computed as follows: 8 hours for the patient plus 4 hours for an escort for OC; 8 hours for the patient for CTC; 4 hours for the patient for US.

[i] Costs are shown for cancer treatment with vs without screening-related downstaging.

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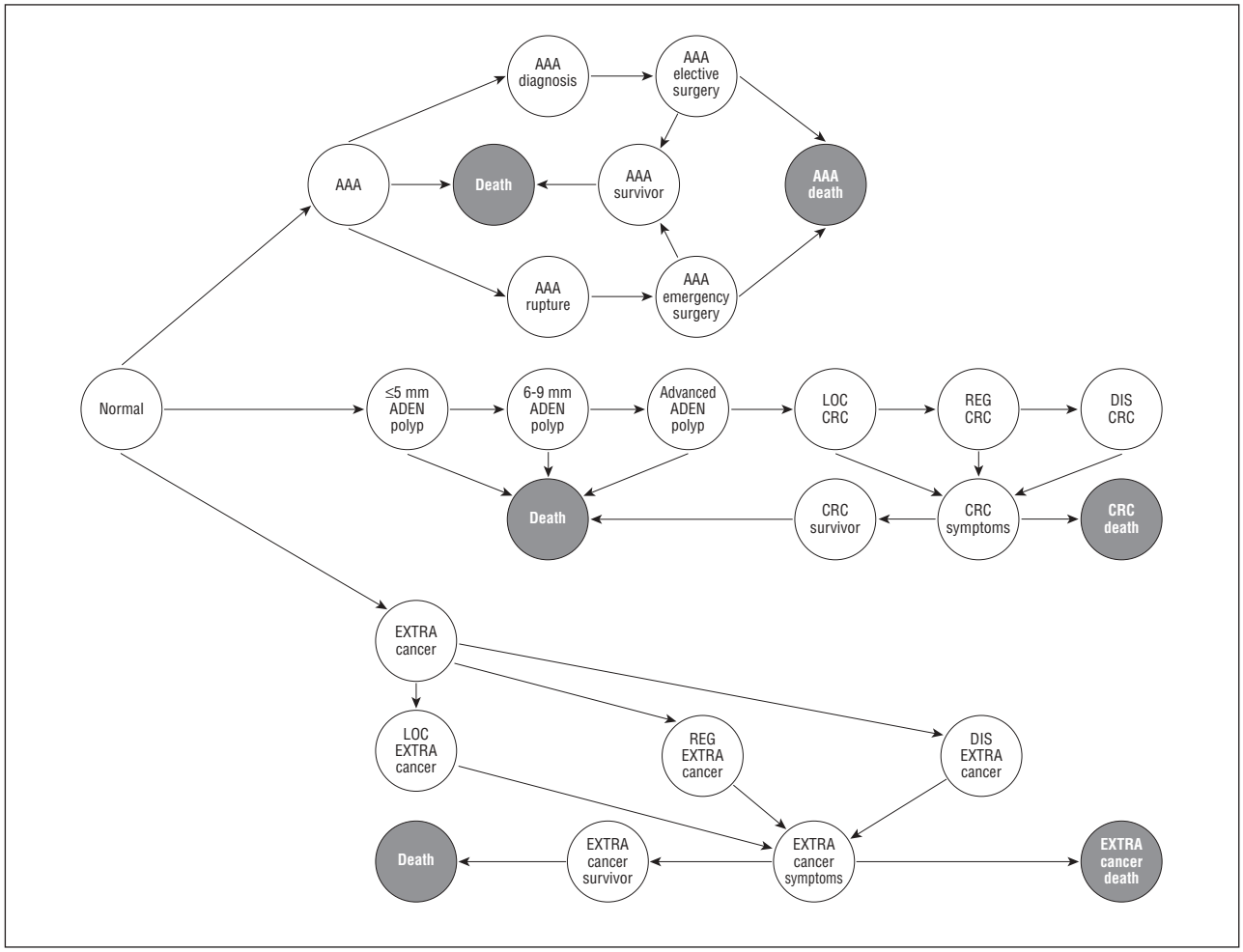

Figure 1. The model has been constructed to simulate the progression from no lesions to death related to colorectal cancer (CRC), abdominal aortic aneurysm (AAA), or extracolonic (EXTRA) cancers through the various phases. The principle health states simulated were as follows: (1) no colorectal neoplasia; hyperplastic polyp; diminutive, small, or large adenomatous (ADEN) polyp; localized (LOC), regional (REG), or distant (DIS) CRC; CRC-related death; (2) nonruptured AAA, ruptured AAA, elective (nonruptured) or emergency (ruptured) related death; and (3) localized, regional, or distant extracolonic malignant neoplasm (each considered separately) and extracolonic cancer–related death.

of 138 205 life-years owing to the overall burden of CRC, AAA, and extracolonic cancers (**Table 2**). **Table 3** shows the outcome of the 3 modeled screening strategies. Overall, CTC was substantially more effective than OC and OC-US screening, gaining an additional 1458 and 462 life-years, respectively. As shown in Table 3, the slightly lower CRC prevention rate of CTC resulted in a relative loss of 834 CRC-related life-years compared with OC and OC-US, which was compensated by the relative gain of 1994 and 996 AAA-related life-years, respectively. This was due to the prevention of an additional 312 and 162 AAA deaths compared with OC and OC-US, respectively. The impact of extracolonic cancer on the efficacy of CTC was fairly minimal, with only 298 total life-years gained compared with the other strategies.

SCREENING PROCEDURES

As shown in Table 3, CTC resulted in a 76% decrease in the use of endoscopic resources compared with OC screening strategies (91 751 vs 374 833). Fewer endoscopic procedures translated into fewer complications (176 vs 616), and the number of OC-related deaths dropped from 22 to 5 when passing from an endoscopic to a radiologic program (Table 3). Unfortunately, this was partially offset by the 36 cases of radiation-induced cancer from CTC, resulting in an estimated 8 deaths.

COSTS

When compared with no screening, each screening strategy resulted in a substantial decrease in CRC-related costs. The AAA-related costs increased by 18% in the OC-US strategy and by 32% in the CTC strategy owing to the additional 536 and 1142 AAA elective surgical procedures, respectively, compared with no screening. As shown in Table 3, the costs related to extracolonic cancers were similar for the CTC and OC-US screening strategies. The major determinant of differences in overall costs between the screening programs was the expenditures for CRC-related screening procedures and their associated complications. The slightly lower assumed costs for CTC compared with OC resulted in a clear advantage for the CTC strategy, which was the least expensive program. The additional

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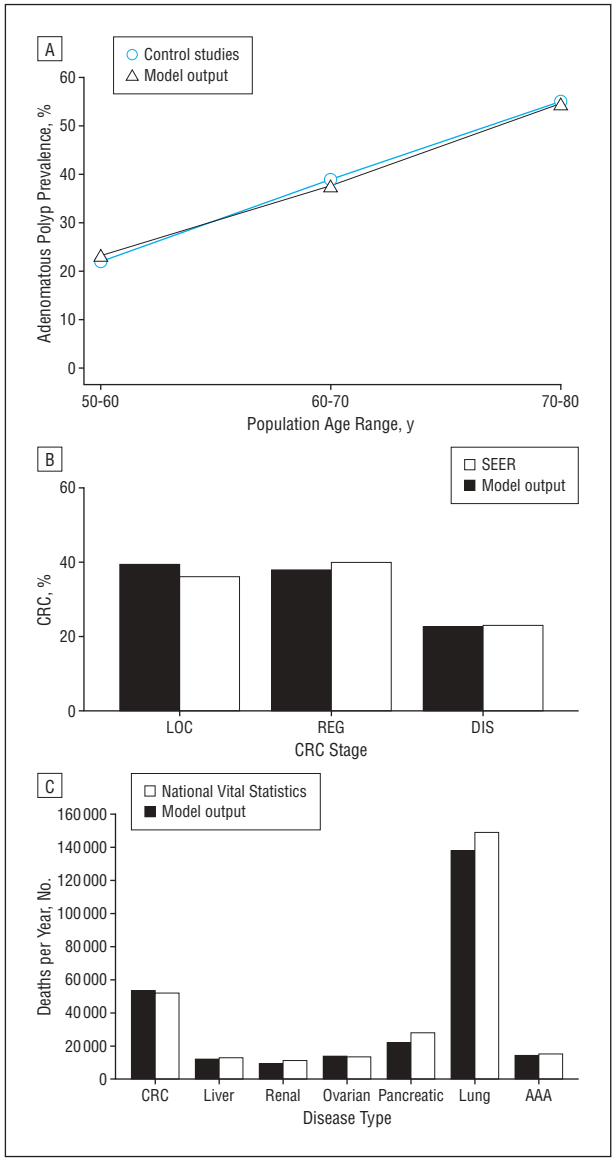

Figure 2. Calibration of the natural history of colorectal neoplasia. A, Validation of the model outputs through comparison with observed values. Prevalence of adenomatous polyps computed by the model compared with that from autopsy and screening studies. B, Stage-distribution of colorectal cancer (CRC) in the simulated population compared with Surveillance, Epidemiology, and End Results (SEER) data.[20] DIS indicates distant; LOC, localized; REG, regional. C, Number of deaths per year for cancers and abdominal aortic aneurysm (AAA) computed by the projection of the model on the population of the United States compared with that retrievable from the National Vital Statistics Report for 2003.[21]

cost of a 1-time US on top of OC screening resulted in the largest budget.

COST-EFFECTIVENESS

As shown in **Table 4**, all 3 strategies were found to be cost-effective screening options, with an ICER compared with no screening that was well below the $100 000 threshold. When comparing CTC with both OC and combined OC-US strategies, CTC was dominant because it was the most cost-effective and clinically effective option.

Table 2. Model Outputs for the Natural History (No Screening) Simulation

Type of Disease	No. Incident Cases	No. Deaths	Life-Years Lost, No. (%)	Cost, $ (%)
CRC	5938	2564	28 471 (21)	204 319 642 (29)
AAA	1367[a]	661	7601 (5)	32 236 404 (4)
Extracolonic cancers	10 436	8061	102 133 (74)	474 409 256 (67)
Total	**17 741**	**11 286**	**138 205**	**710 965 302**

Abbreviations: AAA, abdominal aortic aneurysm; CRC, colorectal cancer.
[a] Defined as number of incident surgical procedures for AAA rupture or for elective treatment of nonruptured AAA.

SENSITIVITY ANALYSIS

Monte Carlo Analysis

When considering the 10th to 90th percentile interval of the ICER of CTC compared with the OC-US and OC strategies, CTC dominated OC-US and OC in 40% and 30% of the 10 000 simulated interactions, respectively, whereas the ICER against OC-US and OC in the remaining 60% of the interactions ranged from $0 to $62 309 and from $0 to $32 214, respectively. This shows that CTC is clearly a competitive option compared with OC-US and OC because in no cases was the ICER even close to the $100 000 threshold.

Variations in Polyp Detection Accuracy

When comparing CTC with the OC strategies, CTC sensitivity for large polyps (those ≥10 mm) is an important consideration, given the relative disparity in the existing literature. As shown in **Figure 3**, a reduction from the baseline value from 85% to 70% for the sensitivity of large polyps was necessary to erase the dominance of CTC over OC-US, mainly because of the reduction in life-years gained from the baseline of 12 127 to 11 624. However, the ICER of OC-US relative to CTC was still higher than $100 000. A further drop in CTC sensitivity for large polyps to 61% was required for OC-US to become a cost-effective option compared with CTC, using an ICER threshold of $100 000. On the one hand, even at very low values of CTC sensitivity, CTC was never dominated by OC-US. On the other hand, only an implausible reduction of CTC sensitivity for large polyps to 44% was necessary to erase the dominance of CTC over OC (Figure 3). Although changes in CTC specificity for colorectal polyps did not practically alter the CRC prevention rate, the associated costs were affected because the increases in unnecessary OC triggered false-positive CTC results. The dominance of CTC over OC was erased by a reduction of CTC specificity from a baseline value of 86% to 70%. However, CTC always remained a cost-effective option compared with OC, even when an implausible CTC specificity of less than 30% was assumed. Owing to the higher costs of the OC-US program, even an unlikely assumption of CTC specificity as low as 35% was unable to eliminate the dominance of CTC over OC-US.

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Table 3. Modeled Outcomes at Baseline Assumptions for the Various CRC Screening Tests[a]

Variable	CTC	OC	OC-US
Cases of CRC prevented	3705	4312	4312
CRC prevention, %	62.4	72.6	72.6
Life-years gained			
CRC	9835	10 669	10 669
AAA	1994	NA	996
Extracolonic cancers	298	NA	NA
Total	**12 127**	**10 669**	**11 665**
Procedures			
CTC	298 562	NA	NA
OC	91 751	374 833	374 833
With polypectomy/biopsy, No. (%)	21 809 (24)	69 075 (19)	69 075 (19)
Without polypectomy/biopsy, No. (%)	69 942 (76)	305 758 (81)	305 758 (81)
US for AAA	NA	NA	86 599
OC-related complications	176[b]	616[c]	616
Bleeding event	105	332	332
Perforation	66	262	262
OC-related deaths	5	22	22
CTC-related perforations	2	NA	NA
CTC-induced cancers	36[d]	NA	NA
CTC-related deaths	8[d]	NA	NA
Costs, $			
CRC	79 425 104	60 241 370	60 241 370
AAA	47 814 565	32 236 404	39 670 728
Extracolonic cancers	475 020 438	474 409 256	474 409 256
CRC screening tests	254 534 932	316 554 877	327 376 885
Total	**856 795 039**	**883 441 907**	**901 698 239**

Abbreviations: AAA, abdominal aortic aneurysm; CRC, colorectal cancer; CTC, computed tomographic colonography; NA, not applicable; OC, colonoscopy; US, abdominal ultrasonography for AAA detection.
[a] Data are given as numbers except where indicated.
[b] Regarded as bleeding, perforation, or death occurring at post-CTC colonoscopy.
[c] Regarded as bleeding, perforation, or death occurring at colonoscopy.
[d] Regarded as cancers related to the radiation exposure due to CTC (see the subsection titled "Screening Procedures" in the "Results" section). Mortality for such radiation-induced cancers was supposed to be equal to that of non–radiation-induced malignant neoplasms.

Table 4. Incremental Cost-effectiveness Ratios of the Various Screening Strategies[a]

Screening Strategy	No Screening	OC	OC-US
CTC	12 025	266, OC-dominated[b]	449, OC-US–dominated[b]
OC-US	16 350	18 338	NA
OC	16 165	NA	NA

Abbreviations: CTC, computed tomographic colonography; NA, not applicable; OC, colonoscopy; US, abdominal ultrasonography for abdominal aortic aneurysm detection.
[a] Data are reported as cost per life-year gained in dollars.
[b] Dominance implies that CTC is less expensive and more effective, resulting in the listed earnings per person.

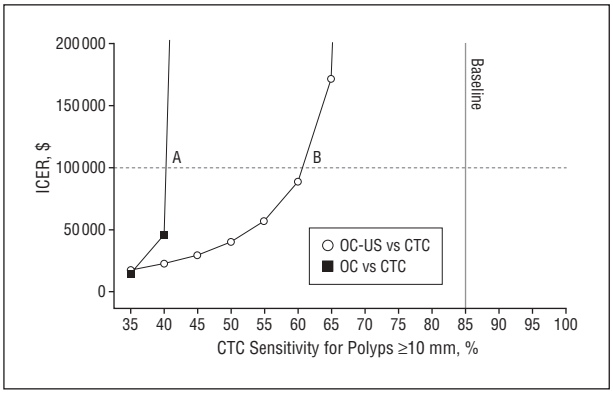

Figure 3. Incremental cost-effectiveness ratio (ICER) of computed tomographic colonography (CTC) compared with colonoscopy and ultrasonography (OC-US) and OC strategies according to CTC sensitivity for large polyps. Data beyond 70% (OC-US) and 44% (OC) sensitivity, including the baseline value of 85%, are not shown because OC-US and OC were dominated at these levels. Below 70% and 44% CTC sensitivity, OC-US and OC become more clinically effective, but only at lower values (points A and B) does the ICER drop below the $100 000 threshold (see the subsection titled "Variations in Polyp Detection Accuracy" in the "Results" section).

Variations in AAA and Extracolonic Cancer Parameters

An increase of AAA rupture risk in the screened group affected the efficacy and cost-effectiveness of both CTC and OC-US screening strategies. However, only an implausible 2-fold increase in the annual, age-specific, AAA rupture risk in the screened group from the baseline value of 0.3% at age 65 years to 0.6% was able to erase the dominance of CTC, with OC-US being slightly more effective in this situation. However, the ICER of OC-US compared with CTC was still above the $100 000 threshold, whereas OC was always dominated by CTC. Assuming such a reduction in efficacy, the number of deaths related to AAA in the screened group would rise from 349 to 647, compared with 661 deaths without screening.

Regarding the sensitivity analysis of extracolonic cancers, we assumed no downstaging for those in a localized stage in order to simulate the opportunistic detection of early cancers by other means. In this case, the net benefit referred to early detection of extracolonic cancers would be reduced by 40% (179 vs 298). Simulating a 0% sensitivity for all the extracolonic cancers, as it may be the case with an ultralow-dose CTC, the CTC strategy would still be more effective (11 829 life-years saved) than the OC strategies.

Variations in Costs

The total cost of CTC evaluation, resulting from the sum of the direct and indirect costs, was $814. As shown in **Figure 4**, an increase in the cost of CTC to $1100 and $1000 was necessary for erasing CTC dominance over OC-US and OC screening, respectively. A further increase to $1300 was required for increasing the ICER of CTC against OC-US above $100 000, whereas, even at the upper level of our sensitivity analysis, CTC always seemed to be a cost-effective option compared with OC (Figure 4). With regard to OC costs, a decrease in the baseline total cost from $1100 to $800 and $500 was re-

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quired to erase CTC dominance over OC-US and to increase the ICER of CTC above $100 000, respectively. On the one hand, although a similar reduction of colonoscopy cost to $900 was sufficient to erase CTC dominance over OC, the ICER of CTC against OC was never higher than $100 000 even in the lowest level of the sensitivity analysis (Figure 4). On the other hand, no meaningful variation in the ICER was found when varying the costs associated with additional imaging for extracolonic findings.

Variation in Compliance

Initial compliance determines how many eligible persons enter the screening program, influencing the number of life-years gained and the costs in a linear fashion. Consequently, it does not influence the cost-effectiveness of any individual program when compared with no screening or another strategy. Similarly, equal variations in compliance to repeated tests did not meaningfully affect the ICER among different techniques. It is unknown what the compliance for US at age 65 years would be for those undergoing OC. As shown in **Figure 5**, a progressive reduction of this US compliance eventually converts the cost and efficacy of OC-US screening into that of simply OC screening (without US). For instance, at compliance values below 70%, OC-US was dominated by CTC, even when a 45% CTC sensitivity for large polyps was simulated.

It has been suggested that CTC should be repeated every 5 years in the screening setting. In this case, the CTC screening program would be more costly ($973 221 204) compared with the OC-US strategy, but also substantially more effective, leading to 13 567 life-years gained. The ICER of CTC every 5 years compared with OC-US and OC would be $37 617 and $30 987, respectively, well under the $100 000 threshold.

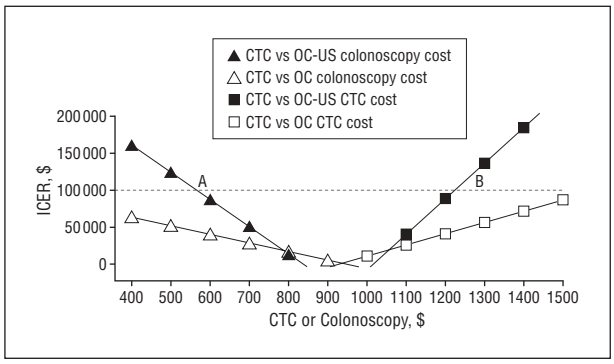

Figure 4. Incremental cost-effectiveness ratio (ICER) between computed tomographic colonography (CTC), on one side, and colonoscopy and ultrasonography (OC-US) and OC strategies, on the other, according to variation in CTC and OC costs (see the subsection titled "Variations in Costs" in the "Results" section). Points A and B indicate the points of intersection where the ICER equals the $100 000 threshold. Data below the zero value along the vertical axis are not shown because this implies dominance of CTC over OC-US or OC.

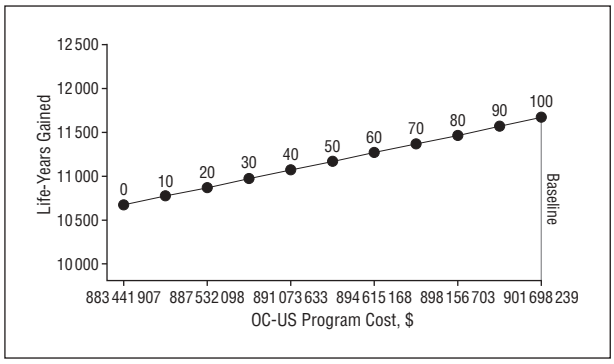

Figure 5. Cost-effectiveness of the colonoscopy and ultrasonography (OC-US) strategy according to compliance for US among those fully compliant for OC screening. Compliance rate values are reported along the line in percentages. Higher values of compliance correspond to increased efficacy, expressed as life-years gained, but also higher costs, because of screening tests and abdominal aortic aneurysm (AAA) surgery. Even at 100% US compliance, the OC-US strategy seems to be less effective and more costly than the computed tomographic colonography program (ie, dominated). The OC-US program cost along the x-axis represents the overall cost of the screening strategy, including the treatment costs of colorectal cancer, AAA, and extracolonic cancers, as well as the cost of the screening tests (Table 3).

COMMENT

When extracolonic evaluation at CTC is brought into consideration, our study demonstrates a clear advantage for CTC over OC for screening. The increased clinical efficacy of CTC in our model was the result of life-years gained by the simultaneous prevention or detection of both AAA and—to a lesser extent—extracolonic cancers. In addition, CTC dominated the combined strategy of OC with 1-time US for AAA detection. This dominance for CTC screening over the OC-related strategies was true not only for the baseline analysis but also for a wide range of input assumptions in the sensitivity analysis. Importantly, both CTC and OC strategies were clearly cost-effective when compared with no screening.

In our current model, extracolonic cancer detection at CTC added relatively little benefit in terms of life-years gained, despite the fact that these extracolonic cancers accounted for 74% of the total potential life-years lost in the unscreened (natural history) group. It is important to note that the input assumptions applied to extracolonic cancers were conservative and very likely underestimated the potential benefit from their early detection at CTC.

The favorable impact of extracolonic evaluation on the cost-effectiveness of CTC in our model was purely related to findings of major clinical relevance, namely AAA and extracolonic malignant neoplasms, which represent only a minority of all extracolonic findings. In practice, most extracolonic findings, such as benign hepatic and renal lesions, are incidental and of no real clinical significance.[7] However, some benign findings, such as hepatic cavernous hemangiomas or adnexal cystic lesions, are indeterminate on low-dose, noncontrast CT and may require further imaging evaluation to confirm benignity. In our experience, the frequency of further imaging workup for unsuspected extracolonic findings is about 6%.[11] The costs associated with this additional imaging workup have been included in our model. Radiologists interpreting screening CTC examinations must be cognizant of both the cost implications and potential psychological stress triggered by recommending further evaluation for extracolonic findings. Only findings with a legitimate potential for clinical relevance should be considered for additional workup.

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One-time US for early detection of AAA has been recommended for men older than 65 years, and this practice is currently reimbursed by Medicare.[37] For this reason, we also simulated a screening approach consisting of OC every 10 years combined with 1-time US. Our findings indicate that this option is clearly superior to a simple OC screening regimen in terms of efficacy and is also a cost-effective option, with an ICER far below $25 000. Although this combined OC-US approach was dominated by CTC at baseline, it was competitive in certain scenarios in the sensitivity analysis. For example, a reduction in CTC sensitivity for large adenomas to 60% allowed OC-US strategy to become a cost-effective alternative to CTC. Although the baseline sensitivity of 85% is below the typical performance seen with current 3-dimensional CTC,[2] a sensitivity of 60% is actually in line with some prior 2-dimensional CTC trials.[38,39] However, it is important to note that the higher efficacy of OC-US screening assumes a very high compliance rate for the US evaluation, which is an untested assumption. Even a relatively small reduction in compliance to 70% was sufficient to erase the advantage of OC-US relative to 2-dimensional CTC.

We also simulated the potential risk of CTC-induced cancer related to the cumulative low-dose radiation exposure from 4 CTC examinations over the 50- to 80-year age range. Using a conservative assumption that real harm does exist, the estimated number of deaths from radiation-induced cancer in the CTC strategy was still less than the number of deaths from endoscopic complications in the OC strategies. However, the actual risk from low-dose radiation is unknown and virtually "unknowable" because any deleterious (or beneficial) effect would essentially represent statistical noise relative to the high baseline incidence of cancer in older adults. According to a recently revised position statement from the Health Physics Society, the risks of health effects from low-dose radiation (defined as 50-100 mSv or less) are "either too small to be observed or are nonexistent."[40(p1)] Of note, the effective dose from a typical CTC study is a full order of magnitude less than this upper threshold used to define "low dose."

The main limitations of our model simulation are related to the uncertainty regarding the effect of early detection of extracolonic findings on life expectancy owing to the lack of controlled clinical studies. Although we assumed an independence among the natural histories of the included diseases, we cannot exclude the existence of some relationship between at least some of them. Accuracy values of unenhanced CTC, although reasonable, are partially based on personal estimates of studies based on contrast-enhanced CT. Similarly, there is further uncertainty in relation to the prevalence of extracolonic findings in a screening setting, the real risk of CTC-related perforation, and the test and treatment costs. Regarding the colorectal adenoma-carcinoma sequence, our assumptions were mainly based on the efficacy showed by endoscopy in cohort studies,[41] no definitive randomized trial being available. Moreover, the natural history of small polyps is still poorly known,[42] and that of large polyps is mainly based on 1 old radiological study[43] with barium enema. Moreover, the existence of alternative pathways of colon carcinogenesis, such as that of the serrated adenoma, or a higher than estimated de novo/polypoid rate could reduce the long-term efficacy simulated in our model.[44,45] However, even wide alterations of these parameters—although meaningfully affecting the incremental cost-effectiveness of each strategy compared with no screening—were unable to alter the relative cost-effectiveness ratio among the included screening strategies because all of them were affected in a similar fashion.

In conclusion, to our knowledge, our study is the first attempt to model the relative cost-effectiveness and clinical efficacy of extracolonic evaluation at CTC screening. Our findings indicate a net benefit from extracolonic evaluation, such that CTC screening dominated the OC screening strategies, even when US evaluation for AAA detection was combined with endoscopic screening.

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Author Contributions: Dr Hassan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hassan, Pickhardt, Zullo, and Di Giulio. *Acquisition of data:* Hassan, Pickhardt, Zullo, and Morini. *Analysis and interpretation of data:* Hassan, Pickhardt, Laghi, Kim, Zullo, and Iafrate. *Drafting of the manuscript:* Hassan, Pickhardt, Zullo, and Morini. *Critical revision of the manuscript for important intellectual content:* Hassan, Pickhardt, Laghi, Kim, Zullo, Iafrate, and Di Giulio. *Statistical analysis:* Hassan, Zullo, Iafrate, and Di Giulio. *Administrative, technical, and material support:* Pickhardt. *Study supervision:* Hassan, Pickhardt, Laghi, and Morini.
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Correction

Error in Byline. In the Original Article by Hassan et al titled "Computed Tomographic Colonography to Screen for Colorectal Cancer, Extracolonic Cancer, and Aortic Aneurysm: Model Simulation With Cost-effectiveness Analysis," published in the April 14, 2008, issue of the *Archives* (2008;168[7]:696-705), there were errors in the names of 2 authors in the byline. "Perry Pickhardt, MD" should be "Perry J. Pickhardt, MD," and "Daniel Kim, MD" should be "David H. Kim, MD."

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