Original Investigation

Variation in Adenoma Detection Rate and the Lifetime Benefits and Cost of Colorectal Cancer Screening
A Microsimulation Model

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IMPORTANCE Colonoscopy is the most commonly used colorectal cancer screening test in the United States. Its quality, as measured by adenoma detection rates (ADRs), varies widely among physicians, with unknown consequences for the cost and benefits of screening programs.

OBJECTIVE To estimate the lifetime benefits, complications, and costs of an initial colonoscopy screening program at different levels of adenoma detection.

DESIGN, SETTING, AND PARTICIPANTS Microsimulation modeling with data from a community-based health care system on ADR variation and cancer risk among 57 588 patients examined by 136 physicians from 1998 through 2010.

EXPOSURES Using modeling, no screening was compared with screening initiation with colonoscopy according to ADR quintiles (averages 15.3%, quintile 1; 21.3%, quintile 2; 25.6%, quintile 3; 30.9%, quintile 4; and 38.7%, quintile 5) at ages 50, 60, and 70 years with appropriate surveillance of patients with adenoma.

MAIN OUTCOMES AND MEASURES Estimated lifetime colorectal cancer incidence and mortality, number of colonoscopies, complications, and costs per 1000 patients, all discounted at 3% per year and including 95% confidence intervals from multiway probabilistic sensitivity analysis.

RESULTS In simulation modeling, among unscreened patients the lifetime risk of colorectal cancer incidence was 34.2 per 1000 (95% CI, 25.9-43.6) and risk of mortality was 13.4 per 1000 (95% CI, 10.0-17.6). Among screened patients, simulated lifetime incidence decreased with lower to higher ADRs (26.6; 95% CI, 20.0-34.3 for quintile 1 vs 12.5; 95% CI, 9.3-16.5 for quintile 5) as did mortality (5.7; 95% CI, 4.2-7.7 for quintile 1 vs 2.3; 95% CI, 1.7-3.1 for quintile 5). Compared with quintile 1, simulated lifetime incidence was on average 11.4% (95% CI, 10.3%-11.9%) lower for every 5 percentage-point increase of ADRs and for mortality, 12.8% (95% CI, 11.1%-13.7%) lower. Complications increased from 6.0 (95% CI, 4.0-8.5) of 2777 colonoscopies (95% CI, 2626-2943) in quintile 1 to 8.9 (95% CI, 6.1-12.0) complications of 3376 (95% CI, 3081-3681) colonoscopies in quintile 5. Estimated net screening costs were lower from quintile 1 (US $2.1 million, 95% CI, $1.8-$2.4 million) to quintile 5 (US $1.8 million, 95% CI, $1.3-$2.3 million) due to averted cancer treatment costs. Results were stable across sensitivity analyses.

CONCLUSIONS AND RELEVANCE In this microsimulation modeling study, higher adenoma detection rates in screening colonoscopy were associated with lower lifetime risks of colorectal cancer and colorectal cancer mortality without being associated with higher overall costs. Future research is needed to assess whether increasing adenoma detection would be associated with improved patient outcomes.

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Colorectal cancer is the second leading cause of cancer deaths in the United States.[1] Screening colonoscopy reduces colorectal cancer mortality risk through detection and treatment of precursor adenomatous or early cancerous lesions,[2-4] but its effectiveness depends on examination quality.[5-7] A currently recommended colonoscopy quality indicator, the adenoma detection rate (ADR), has been found to vary at least 3-fold across examining physicians.[8-10] A recent large US study found that this variation is associated with patient outcomes. Compared with patients of physicians with the highest ADRs, patients of physicians with the lowest ADRs had a nearly 50% higher risk of colorectal cancer and a 60% higher risk of fatal disease within 10 years of follow-up after colonoscopy.[10] This suggests that higher adenoma detection is associated with both better disease detection and management. However, little is known about the consequences of different levels of ADRs for the lifetime benefits, risks, and costs in a program using colonoscopy as the initial and primary screening test in an average-risk population. Higher ADRs may accrue mostly from increased detection of small low-risk polyps, resulting in an increased number of subsequent surveillance colonoscopies, and complications from polyps that may never cause fatal disease. Thus, any benefits of higher ADRs may be outweighed by the corresponding harms.[11]

In the present study, we evaluated various outcomes for a colonoscopy-based colorectal cancer screening strategy according to different adenoma detection rate levels, including lifetime colorectal cancer incidence and mortality, the number of colonoscopies and related complications, and screening and treatment costs.

Methods

We used microsimulation modeling of screening in a US population cohort with community-based data on ADR variation and cancer risk. This study was approved by the Kaiser Permanente Northern California institutional review board, which waived the requirement for informed consent, and was conducted as part of the US National Cancer Institute–funded consortium Population-Based Research Optimizing Screening through Personalized Regimens, which aims to conduct multisite, coordinated, transdisciplinary research to evaluate and improve cancer screening.

Data

Physician-level (ADRs) and patient-level (age, sex, race/ethnicity, cancer diagnosis) data were gleaned from an integrated health care delivery system.[10] The data for this study were confined to screening colonoscopies performed by 136 gastroenterologists between January 1, 1998, and December 31, 2010. Outcomes were ascertained in the 6-month to 10-year period after initial colonoscopy through December 31, 2010. The screening indication excluded patients who had prior adenomas or colorectal cancer; inflammatory bowel disease within 10 years; colonoscopy within 10 years and sigmoidoscopy within 5 years; positive fecal hemoglobin test within 1 year; or abdominal symptoms within 6 months. Adenoma detection rates, the proportion of a physician's screening colonoscopies that detect at least 1 histologically confirmed adenoma, ranged from 7.35% to 52.51%; the averages were 15.32% (range, 7.35%-19.05%) for quintile 1, 21.27% (range, 19.06%-23.85%) for quintile 2, 25.61% (range, 23.86%-28.40%) for quintile 3, 30.89% (28.41%-33.50%) for quintile 4, and 38.66% (33.51%-52.51%) for quintile 5.

Microsimulation Model

The Microsimulation Screening Analysis-colon (MISCAN-colon) model is part of the Cancer Intervention and Surveillance Modeling Network sponsored by the US National Cancer Institute and has informed US Preventive Services Task Force screening recommendations.[12] The model is described extensively in the eAppendix in the Supplement. In short, a MISCAN-colon analysis generates an average-risk screening population with similar life expectancy and risk of colorectal cancer as the US population. It specifies, with individual variability, the risk of developing 1 or more colorectal neoplasia through the adenoma-carcinoma sequence, and potential cancer-related reductions in life expectancy. Different screening scenarios can be evaluated. The modeled effectiveness of screening shows good concordance with observed interval cancer rates from trials of fecal occult blood tests and endoscopy (eFigure 4 in Supplement).[13-16]

Natural History of Colorectal Cancer

The MISCAN-colon model assumes that colorectal cancer develops progressively from small (≤5 mm) through medium (6-9 mm) or large adenomas (≥10 mm). An early-stage tumor may progress to an advanced-stage tumor without symptoms or may become symptomatic during any stage and be clinically diagnosed. Some patients die of the disease and lose life-years, while others die of competing causes before or after developing cancer. Serrated adenomas are not modeled distinctly from conventional adenomas.[17] Adenoma prevalence and age-, stage- and location-specific incidence of colorectal cancer in the absence of screening used data from the era before screening became commonly used (**Table 1**, eAppendix in the Supplement). Age-, stage- and location-specific survival used cancer registry data on patients diagnosed in 2000 through 2003 with follow-up to 2010; mortality from competing causes was estimated from 2010 US lifetables.

Performance Characteristics of Colonoscopy

The modeled effectiveness of colonoscopy screening depends on assumptions regarding its completeness and sensitivity for adenomatous lesions (Table 1). For this study, we used observed data from Kaiser Permanente to derive sensitivities for colonoscopy at the 5 ADR quintiles, while assuming no underlying differences in adenoma prevalence.[27]

In a separate analysis, patient populations in each quintile were simulated using the age distribution at screening (eMethods in Supplement). We derived 5 different sets of parameters for per-lesion sensitivity by polyp size to reproduce the average ADR for each quintile. These were

Table 1. Key Modeling Assumptions

Input Parameter	Assumption		Source
	Base Case	Probabilistic Sensitivity Analysis[a]	
All-cause mortality	US lifetables		CDC 2010
Adenoma onset	Age-dependent (nonhomogeneous Poisson)	Uniform distribution (−20% + 20%)	
Adenoma progression			
State transitions	Age-dependent	Uniform distribution (−10% + 10%)	
State duration, (total), y	Exponential (λ = 130)	λ-Uniform distribution (−10% + 10%)	
Cancer progression (preclinical)			
Stage transitions	Age-dependent	Uniform distribution (−10% + 10%)	
Stage durations, y	Exponential (λ = 2.5)	λ-Uniform distribution (−10% + 10%)	
Colorectal cancer			
Incidence (without exposure to screening)	Age-, stage-, location-dependent		SEER 1975-1979
Survival	Age-, stage-, location-dependent		SEER 2000-2010
Colonoscopy quality			
Sensitivity, %[b]	ADR quintile-dependent:	β Distribution (SE)	
Adenomas			
0-5 mm	14.7-29.6-41.0-66.2-98	3.5	
6-9 mm	39.6-65.8-85.0-94.3-98	3.5	Van Rijn et al,[5] 2006
≥10 mm	88.0-92.2-95.0-96.8-98	2.5	Van Rijn et al,[5] 2006
Malignant neoplasia	98	2.5	
Specificity, %[c]	85	5	Gohel et al,[18] 2014; Williams et al,[19] 2012
Complete colonoscopy examination, %[d]	98	2.5	Imperiale et al,[20] 2000; Liberman et al,[21] 2000
Complication rates, %			Warren et al,[22] 2009; Gatto et al,[23] 2003
With polypectomy	Age-dependent (50-100 y):	Log-normal distribution (SE), %	
Serious GI	0.2-2.9	10	
Fatal	0.0033	50	
Other GI	0.2-2.6	10	
Cardiovascular	0.1-2.5	10	
Without polypectomy[e]			
Costs, US $[f]			
Colonoscopy			CMS 2007[24]
Without polypectomy	899	5	
With polypectomy	1140-1270 for ADR quintiles 1-5	5	
Complication	6129		CMS 2007[25]
Per life-year with cancer care[g]	Stage-dependent (I-IV)	Log-normal distribution (SE), %	CMS 2007[26]
Initial year	37 185-78 876	1.1-1.9	
Ongoing	3092-12 350	4.4-5.7	
Terminal year	64 693-89 600	1.2-2.2	
Terminal year	19 427-50 552	8.4-10	

Abbreviations: ADR, adenoma detection rate; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare & Medicaid Services; GI, gastrointestinal; SEER, Surveillance Epidemiology and End Results program.

[a] In multiway probabilistic sensitivity analysis, model parameters varied randomly by uniform, β, or lognormal distributions. To limit the degrees of freedom, some parameters were assumed to be correlated: sensitivity for small adenomas with sensitivity for medium adenomas, sensitivity for large adenomas with sensitivity for cancer, all complication types, costs of colonoscopy with and without polypectomy, and all treatment costs.

[b] Sensitivity was defined as the probability of detecting an adenoma at examination.

[c] The lack of specificity indicates how many examinations that did not detect adenomatous lesions included polypectomy for nonadenomatous lesions.

[d] Colonoscopy was considered complete if the cecum was reached. For incomplete examinations, the end point was assumed to be distributed uniformly over the colon and rectum.

[e] We assumed no higher risk for colonoscopy without polypectomy. Complication risks for polypectomy were assumed to increase exponentially with age. The fatal perforation rate was derived from estimates of the incidence of perforation and case-fatality for perforation.[22,23]

[f] Screen and treatment costs include patient time but not cost of travel, lost productivity, or unrelated health care in added life years. Patient time was valued at the median US wage in May 2013 ($16.87 per hour). We included 8 hours of patient time for colonoscopies and used previous estimates for the costs of life-years with cancer care.[26]

[g] Colorectal cancer care included (1) initial, 12 months after diagnosis; (2) terminal, the last 12 months of life; and (3) continuing, in-between months. Terminal care was distinguished by patients' dying of cancer or another cause. For those surviving less than 24 months, the final 12 months were allocated to the terminal and the rest to the initial care phase.

constrained by assuming that (1) sensitivity for cancer was 98% across all quintiles; (2) sensitivity for medium to large adenomas varied less than for small adenomas and increased according to a fixed rule from the lowest to the highest quintile (fixed-detection likelihood (sensitivity/[1−sensitivity]) ratios for adjacent quintiles) while matching estimates for average practice in the middle quintile (85% for medium adenomas, 95% for large adenomas)[5]; (3) maximum sensitivity for adenomas was 98%. Sensitivity for adenomas was then varied to match ADR values with 0.1-point precision. The estimates were independent of adenoma location. The data on cancer diagnoses after colonoscopy were compared with the cancer incidence predicted by the model.

Complication Risk of Colonoscopy

Adverse events for colonoscopy including polypectomy used age-specific complication rates derived from published literature (Table 1).[22,23]

Costs of Screening and Treatment

The approximate societal costs of colonoscopy, complications, and colorectal cancer treatment were based on 2007 Medicare payment rates and co-payments (Table 1).[24-26] All costs included patient time valued at the median US wage in 2013, updated to December 2013 based on the general consumer price index.[28] Costs of colonoscopy with polypectomy included a variable component for polyp resection and pathology based on number of polyps resected.

Outcomes

Outcomes included were colorectal cancer incidence and mortality, years of life lost, number of colonoscopies, complications, and the costs of screening and treatment in unscreened persons and in those screened according to ADR quintiles. In addition, we estimated the average outcome differences associated with each 5 percentage-point increase in ADRs using linear regression. Outcomes were discounted to 2010 at a fixed annual rate of 3% and reported with uncertainty ranges.

Analysis

We simulated a US population cohort of 10 million men and women born January 1, 1960. For patients reaching the age of 50 without having colorectal cancer diagnosed (9.4 million), we compared the outcomes of no screening or of screening colonoscopy at ages 50, 60, and 70 years by physicians from 1 of the 5 ADR quintiles.[12] Patients with adenomas detected were assumed to receive surveillance according to current US guidelines.[29] We assumed that the same physician performed all screening and surveillance colonoscopies for each individual patient, and thus, ADR exposure level remained constant during the life-course.

Multiway probabilistic sensitivity analysis was conducted to derive 95% confidence intervals for all outcomes evaluated.[30,31] In 1000 simulation runs of 10 million persons, we varied 13 key parameters along uniform, β, or log-normal distributions (Table 1).

Sensitivity Analysis

We evaluated the robustness of results using several alternative modeling scenarios. Between-quintile ADR variation was attributed either entirely to examination sensitivity for small lower-risk adenomas; equally to examination sensitivity for small, medium, and large adenomas; or partially to examination sensitivity and to adenoma prevalence or colonoscopy completion rates (≈ 1% higher per percentage-point >ADR). Patients with adenomas received either more intensive or no surveillance. We also evaluated a 50% increased colonoscopy cost level and undiscounted outcomes.

To evaluate data uncertainty, we performed a bootstrap analysis on the association between observed average ADR and interval cancer rates across quintiles and contrasted the resulting weak and strong association samples (2.5th-97.5th percentile) to the modeling scenarios.

Statistical Software

For microsimulation modeling, we used Delphi 7.0 (Borland Software Corp). Additional data analyses were performed using Stata 13.1 (StataCorp).

Results

A total of 57 588 screening colonoscopies were performed by 136 physicians from 1998 through 2010 (**Table 2**). After exclusion of patients with less than 6 months' follow-up (n = 7718), there were 179 682 person-years of follow-up. Interval colorectal cancer incidence per 100 000 person-years varied from 66.6 (95% CI, 43.2-97.0) in quintile 1 to 39.0 (95% CI, 22.7-62.4) in quintile 4, but was 49.7 (95% CI, 27.8-81.9) in quintile 5.

Simulated Interval Cancer Incidence

To replicate the average detection rate per quintile, colonoscopy sensitivity was varied according to adenoma size from: 14.7% in quintile 1, 41.0% in quintile 3 to 98% in quintile 5 for small adenomas; 39.6% to 98% for medium adenomas; and 88.0% to 98% for large adenomas (see Table 1 for estimates per quintile). The model closely reproduced observed colorectal cancer incidence in the lower 4 quintiles, but underestimated incidence in the upper quintile (eFigure 7 in Supplement).

Lifetime Colorectal Cancer Outcomes Without and With Screening

The model estimated that the average overall life expectancy without exposure to screening and surveillance was at age 81.1 years, the lifetime colorectal cancer risk was 34.2 per 1000 (95% CI, 25.9-43.6), the lifetime colorectal cancer mortality risk was 13.4 per 1000 (95% CI, 10.0-17.6), and the years of life lost due to colorectal cancer was 138.7 life-years per 1000 (95% CI, 103.0-184.0), which is about 10.4 years per cancer death (**Table 3**). Among screened patients, simulated lifetime risk of colorectal cancer incidence was on average 19.1 per 1000 (95% CI, 14.3-24.8), mortality was 3.8 per 1000 (95% CI, 2.8-5.2); and years of life lost due to colorectal cancer was 42.7 (95% CI, 30.9-57.5) life-years per 1000 patients.

Table 2. Kaiser Permanente Northern California Patient and Physician Characteristics According to Quintile of Adenoma Detection Rate

	Quintiles of Adenoma Detection Rate					Total
Variable	1	2	3	4	5	
No. of physicians	27	27	28	27	27	136
Adenoma detection rate, %[a]						
Mean	15.32	21.27	25.61	30.89	38.66	26.45
Median (range)	16.56 (7.35-19.05)	21.50 (19.06-23.85)	25.70 (23.86-28.40)	30.96 (28.41-33.50)	38.86 (33.51-52.51)	25.70 (7.35-52.51)
Patient characteristics						
No. of screened adults	11 799	10 579	10 978	12 918	11 314	57 588
Cancer diagnosed within 6 mo	114	93	106	176	119	608
≤6 mo of follow-up	1452	1253	1179	1421	1805	7110
Proportion men, % (95% CI)	42.8 (34.6-51)	43.4 (36-50.8)	44.1 (36.2-51.9)	45.0 (37.3-52.7)	44.5 (37.1-51.9)	44.0 (36.1-51.8)
Age, mean (95% CI), y	61.3 (59.3-63.2)	61.3 (59.5-63.1)	62.0 (59.1-64.9)	62.0 (60.1-64)	61.9 (59.5-64.3)	61.7 (59.3-64.1)
Age groups, y, %						
50-54	25.6	25.4	23.5	23.6	24.0	24.4
55-59	21.4	20.6	19.9	19.8	19.8	20.3
60-64	20.7	21.9	20.7	20.2	20.8	20.8
65-69	14.9	15.4	15.0	16.2	15.4	15.4
70-74	9.7	9.2	11.4	10.5	10.8	10.3
75-84	6.9	6.9	8.9	8.6	8.4	7.9
≥85	0.8	0.7	0.7	1.0	0.8	0.8
Race/ethnicity, %						
Non-Hispanic white	69.0	73.0	67.9	65.7	66.5	68.3
Hispanic	5.9	5.5	8.2	7.1	8.1	7.0
Non-Hispanic black	7.8	5.3	4.4	4.5	4.0	5.2
Asian	7.4	7.8	10.2	14.5	13.0	10.7
Native American	0.3	0.3	0.4	0.4	0.3	0.4
Other	2.3	2.2	2.5	2.5	2.9	2.5
Unknown	7.2	5.8	6.4	5.4	5.2	6.0
Patients with adenomas detected, No.[a]	1808	2250	2811	3991	4374	15 234
Person-years of follow-up[b]	39-033	33-251	33-564	43-635	30-200	179-682
Interval cancers diagnosed[c]	26	18	14	17	15	90
Incidence per 100 000 per person-year (95% CI)	66.6 (43.2-97.0)	54.1 (32-85.3)	41.7 (23.1-70.8)	39.0 (22.7-62.4)	49.7 (27.8-81.9)	50.1 (40.3-61.6)

[a] Including only histologically confirmed adenomas by pathologists.

[b] Patients were followed up from the date of their index colonoscopy until the first of the following events: negative follow-up colonoscopy, diagnosed cancer, death, or departure from membership, 10-year follow-up, or study end (December 31, 2010).

[c] Interval cancers were colorectal adenocarcinomas diagnosed 6 months or more and 10 years or less of the index colonoscopy.

The modeled risks were inversely related to the level of adenoma detection (Table 3). The simulated lifetime risk of colorectal cancer per 1000 was 26.6 (95% CI, 20.0-34.3) for patients of physicians in quintile 1 and was monotonically lower for subsequent quintiles; in quintile 5, the simulated lifetime colorectal cancer risk was 12.5 (95% CI, 9.3-16.5). Compared with quintile 1, simulated lifetime risk of colorectal cancer was on average 11.4% (95% CI, 10.3%-11.9%) lower for each 5 percentage-point increase in ADRs (**Figure**). Similarly, the simulated lifetime risk of colorectal cancer death per 1000 decreased from 5.7 (95% CI, 4.2-7.7) in quintile 1 to 2.3 (95% CI, 1.7-3.1) in quintile 5 as did the associated years-of-life lost from 61.4 (95% CI, 44.4-82.9) in quintile 1 to 27.0 (95% CI, 19.5-36.2) in quintile 5. The simulated lifetime risk of colorectal cancer death was on average 12.8% lower (95% CI, 11.1%-13.7%) for every 5 percentage-point increase in physician ADRs.

Colonoscopy Volume and Complications

The model's total estimated number of colonoscopies per 1000 patients was progressively higher from quintile 1 (2777, 95% CI, 2626-2943) to quintile 5 (3376, 95% CI, 3081-3681) (**Table 4**), an average of 4.6% (95% CI, 3.6%-5.7%) for every 5-point increase in ADRs (Figure). This difference was related to more frequent surveillance in patients of physicians with higher ADRs. The simulated lifetime risk per 1000 of serious gastrointestinal complications such as postpolypectomy bleeding and perforation was also higher from quin-

Table 3. Modeling Results: Outcomes Associated With Colonoscopy Screening According to Quintile of Adenoma Detection Rate[a,b]

Lifetime Health Outcomes per 1000 Patients	Screening, Mean (95% CI)[c]					
		Quintiles of Adenoma Detection Rate				
	None	1	2	3	4	5
Colorectal cancer outcomes						
Cases	34.2 (25.9-43.6)	26.6 (20-34.3)	21.9 (16.3-28.1)	19.0 (14-24.7)	15.6 (11.6-20.3)	12.5 (9.3-16.5)
Advanced cancer cases[d]	16.8 (12.3-22.6)	7.3 (5.2-9.9)	5.6 (4-7.7)	4.7 (3.4-6.3)	3.7 (2.6-5.1)	2.9 (2.1-3.9)
Deaths	13.4 (10-17.6)	5.7 (4.2-7.7)	4.5 (3.2-6)	3.7 (2.7-5)	3.0 (2.1-4)	2.3 (1.7-3.1)
Years of life lost[e]	138.7 (103-184)	61.4 (44.4-82.9)	49.2 (35.6-66.1)	41.8 (30.4-55.9)	33.9 (24.4-46.3)	27.0 (19.5-36.2)
Effectiveness of Screening						
Prevented cancer						
Cases		7.7 (5.4-10.3)	12.3 (9.1-16.2)	15.3 (11.4-19.8)	18.7 (14-24)	21.7 (16.2-27.8)
Deaths		7.7 (5.8-10)	8.9 (6.7-11.6)	9.6 (7.2-12.6)	10.4 (7.8-13.8)	11.1 (8.2-14.6)
Years of life saved		77.3 (58-102.3)	89.5 (66.5-117.1)	96.8 (71.8-127.4)	104.8 (78.2-139.1)	111.7 (82.8-148.4)

[a] All outcomes were discounted to 2010 at a fixed rate of 3% per year. For undiscounted outcomes see eTable 2.

[b] Adenoma detection rate quintiles were derived from 57 588 colonoscopies performed by 136 gastroenterologists. The averages (and ranges) of ADR for quintiles 1 through 5 were 15.32% (7.35%-19.05%), 21.27% (19.06%-23.85%), 25.61% (23.86%-28.40%), 30.89% (28.41%-33.50%), and 38.66% (33.51%-52.51%), consecutively.

[c] 95% confidence intervals were derived by multiway probabilistic sensitivity analysis.

[d] Advanced-stage cancers were stage III-IV according to the 5th edition of the Cancer Staging Manual from the American Joint Committee on Cancer.[32]

[e] Years of life lost to the disease were obtained by subtracting the simulated lifetimes with disease from the simulated lifetimes based on other-cause mortality rates.

tile 1 (2.2, 95% CI, 1.5-3.1) to quintile 5 (3.2; 95% CI, 2.3-4.4), as were the overall complications (6.0, 95% CI, 4.0-8.5 to 8.9, 95% CI, 6.1-12.0) and fatal complications (0.03 to 0.05). Overall, the simulated risk of complications was on average 9.8% (95% CI, 7.5%-13.2%) higher for every 5 percentage-point increase in ADRs.

Estimated Costs of Screening and Treatment

For quintile 1, estimated colonoscopy-related costs in US dollars per 1000 patients were $2.7 million (95% CI, $2.4-$3.1 million), and the estimated treatment costs were $2.4 million (95% CI, $1.8-$3.1 million), for an estimated total of $5.2 million (95% CI, $4.4-$6.0 million) without adjustment and $2.1 million (95% CI, $1.8-$2.4 million) with adjustment for the estimated costs without screening (Table 4). For higher ADR quintiles, estimated colonoscopy costs were higher, but estimated treatment costs were lower, for lower estimated total costs ($4.9 million, 95% CI, $4.1-$5.6 million) and net screening costs ($1.8 million, 95% CI, $1.3-$2.3) in quintile 5. Estimated net screening costs were on average 3.2% lower (95% CI, 0.8%-6.4% million) for every 5 percentage-point increase in ADRs.

Sensitivity Analyses

The simulations were stable to various assumptions regarding colorectal carcinogenesis, colonoscopy efficacy, and surveillance intervals (Figure). Although simulated costs were more unstable, the absolute corresponding cost differences were small (eTable 1 in the Supplement). Without discounting, the estimated benefits of higher ADR were approximately twice as large as with discounting (eTables 2 and 3 in the Supplement).

For quintiles 1 to 4, strong- and weak-association scenarios from the bootstrap analysis for observed ADR and cancer incidence data were within the predicted ranges of the sensitivity analysis models (eFigure 7B in the Supplement).

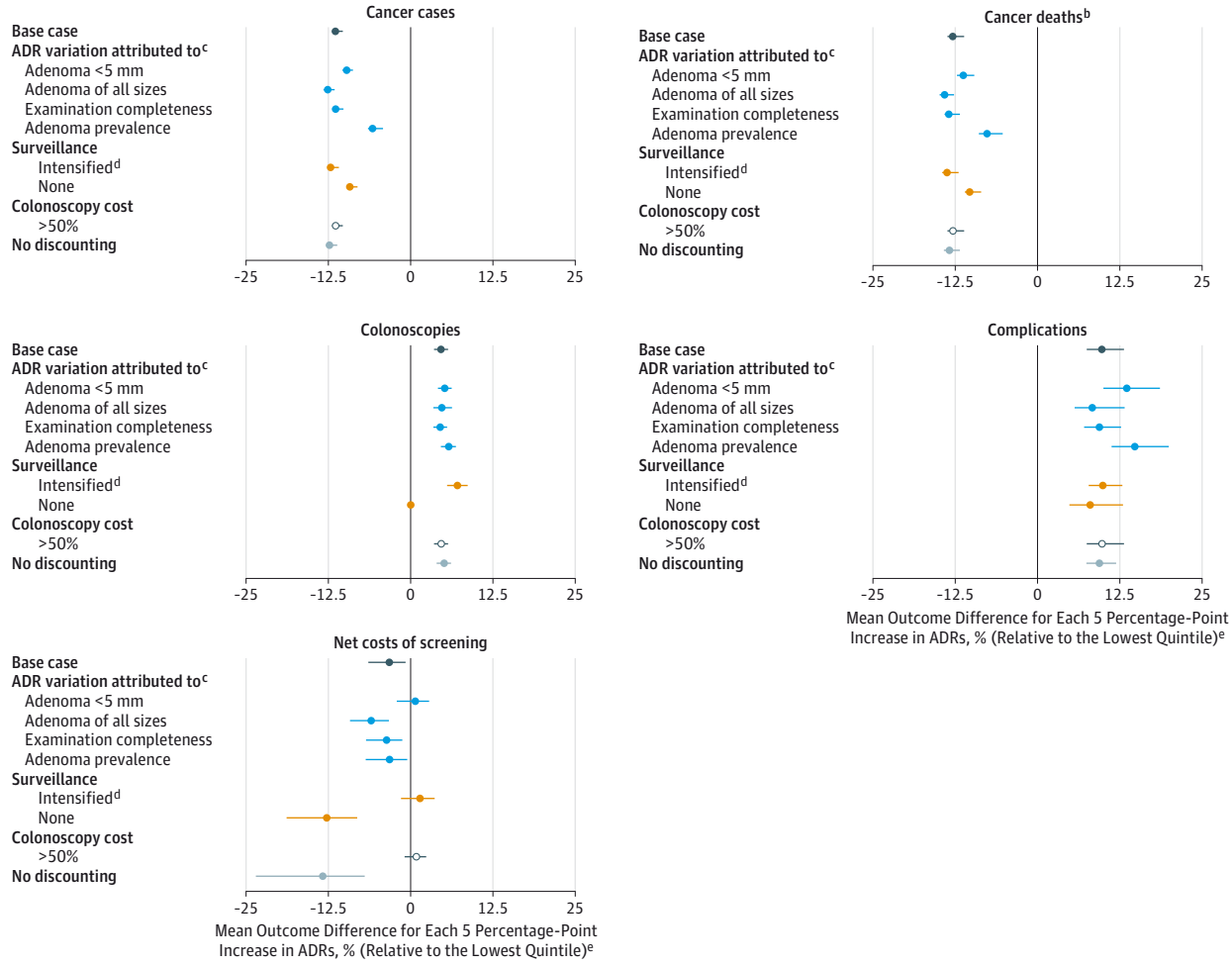
Discussion

This study used data from a large community-based US health care system in a microsimulation model to estimate the lifetime outcomes and costs of colonoscopy screening at different levels of adenoma detection.[10] Our results suggest that higher adenoma detection rates may be associated with up to 50% to 60% lower lifetime colorectal cancer incidence and mortality without higher net screening costs despite a higher number of colonoscopies and polypectomy-associated complications.

The differences in observed interval colorectal cancer incidence were assumed to result from differences in the sensitivity of the examination, particularly for small- to medium-sized adenomas. However, ADR may act as a surrogate for other aspects of colonoscopy quality, such as the test completeness, adequacy of lesion resection, and removal of more aggressive lesions such as sessile serrated polyps.[33] Although some of these alternative explanations were evaluated in sensitivity analyses, with similar long-term results (Figure), we could not establish which factors accounted for the observed differences (eFigure 7B in the Supplement) and whether others might be involved.

The frequency and intensity of surveillance of patients with adenoma may also contribute to patient outcome differences because higher ADRs increase the number of patients for active

Figure. Sensitivity Analysis of the Adenoma Detection Rate (ADR)–Outcome Relationship for Various Modeling Scenarios[a]



[a] 95% CIs, which were derived by multiway probabilistic sensitivity analysis, were relatively narrow because we applied the same assumptions for the natural history of colorectal cancer to all patients (Table 1). Colonoscopy sensitivity was the only assumption varied independently for each quintile. Data markers represent means.

[b] Results were similar for years of life lost to cancer.

[c] We evaluated 4 alternative causal models for observed cancer incidence differences across quintiles: in scenario 2, all variation in ADRs was attributed to sensitivity of colonoscopy for adenomas smaller than 5 mm, which varied from 5.4%, lowest, to 98%, highest quintile; in scenario 3, all ADR variation was attributed equally to sensitivity for small, medium, and large adenomas, which varied from 26.0% to 98%; in scenario 4, it was assumed that the rate of completeness of colonoscopy along with differences in colonoscopy sensitivity accounted for the observed ADR-variations, varying from 75% to 98%; and scenario 4, adenoma prevalence up to a relative 25% higher with higher ADR was assumed.

[d] Under intensified surveillance, we assumed that all patients with adenomas detected at colonoscopy underwent surveillance at 3 years after the procedure and that patients with a negative surveillance colonoscopy underwent surveillance at 5 years. For reference, in the base-case analysis, patients with adenomas found at colonoscopy were referred for surveillance after 3 or 5 years, depending on the number and size of the adenomas detected. Patients with no surveillance colonoscopy were referred for a follow-up colonoscopy in 5 or 10 years, depending on whether the preceding interval was 3 or 5 years.

[e] The mean differences in simulated outcomes were derived by linear regression and presented relative to the model outcomes for ADR quintile 1 ($5 \times \beta_{ols}/\text{outcome}_{q1}$).

surveillance.[29] However, sensitivity analyses indicated that surveillance did not account for the simulated survival benefits for patients of physicians with higher ADRs (Figure). Future research is needed to assess whether the current intensity of surveillance is still appropriate if test sensitivity further increases.

Prior studies have shown an inverse relationship between ADR level and the patient's risk of colorectal cancer up to 5 years after colonoscopy.[34-36] A recent large study found that patients of physicians in the highest ADR quintile had a 48% lower disease risk and a 62% lower mortality risk compared with the lowest quintile.[10] Adenoma detection rates may relate to patient outcomes over a lifetime of colonoscopy screening and surveillance. Our model estimated that discounted lifetime incidence and mortality risks averaged 11% to 13% lower for every 5-point higher ADR, which translates to overall differences of 53% to 60% between the lowest and highest quintiles. Higher ADRs were associated in the model with up to 34.4 additional life-years saved per 1000 patients, which represents about 10 years per prevented cancer death, 2 weeks per average patient, and one-third of the maximum

Table 4. Modeling Results: Resources and Complications for Colonoscopy Screening According to Quintile of Adenoma Detection Rate[a]

Resources and Complications per 1000 Patients	Screening, Mean (95% CI)[b]					
		Quintiles of Adenoma Detection Rate				
	None	1	2	3	4	5
Screening Resources Used						
Colonoscopies						
Total		2777 (2626-2943)	2980 (2786-3197)	3094 (2873-3329)	3252 (2985-3533)	3376 (3081-3681)
Screening		2008 (1972-2041)	1948 (1901-1993)	1912 (1858-1964)	1857 (1794-1921)	1807 (1736-1885)
Surveillance[c]		769 (584-968)	1032 (796-1290)	1182 (915-1465)	1395 (1074-1728)	1569 (1204-1935)
With polypectomy (screening and surveillance)		956 (742-1176)	1187 (938-1424)	1312 (1045-1553)	1479 (1188-1733)	1599 (1284-1862)
Colonoscopy-related GI tract complications		6.0 (4-8.5)	7.4 (5-10.1)	8.0 (5.4-10.8)	8.6 (5.9-11.7)	8.9 (6.1-12)
Serious		2.2 (1.5-3.1)	2.7 (1.8-3.7)	2.9 (2-4)	3.2 (2.2-4.3)	3.2 (2.3-4.4)
Fatal[d]		0.03 (NA)	0.04 (NA)	0.04 (NA)	0.05 (NA)	0.05 (NA)
Other		2.2 (1.4-3.1)	2.6 (1.8-3.6)	2.8 (2-3.9)	3.1 (2.1-4.2)	3.2 (2.2-4.3)
Cardiovascular complications		1.6 (1.1-2.3)	2.0 (1.4-2.7)	2.1 (1.5-2.9)	2.3 (1.6-3.2)	2.4 (1.7-3.2)
Financial Resources Used (US$ in millions)[e]						
Costs						
Total screening and treatment	3.1 (2.3-4)	5.2 (4.4-6)	5.1 (4.3-5.9)	5.0 (4.2-5.8)	4.9 (4.2-5.7)	4.9 (4.1-5.6)
Screening		2.8 (2.5-3.1)	3.1 (2.7-3.4)	3.2 (2.8-3.7)	3.5 (3-4)	3.7 (3.2-4.2)
Colonoscopy		2.7 (2.4-3.1)	3.0 (2.6-3.4)	3.2 (2.8-3.6)	3.4 (3-3.9)	3.6 (3.1-4.2)
Complication		0.0 (0-0.1)	0.0 (0-0.1)	0.0 (0-0.1)	0.1 (0-0.1)	0.1 (0-0.1)
Treatment	3.1 (2.3-4)	2.4 (1.8-3.1)	2.0 (1.5-2.6)	1.7 (1.3-2.3)	1.5 (1.1-1.9)	1.2 (0.9-1.5)
Net screening[f]		2.1 (1.8-2.4)	2.0 (1.6-2.4)	1.9 (1.5-2.3)	1.9 (1.4-2.3)	1.8 (1.3-2.3)

Abbreviations: ADR, adenoma detection rate; GI, gastrointestinal; NA, not assessed.

[a] All outcomes were discounted to 2010 at a fixed rate of 3% per year. For undiscounted outcomes see eTable 3 in the Supplement. Adenoma detection rate (ADR) quintiles were derived from 57 588 colonoscopies performed by 136 gastroenterologists in Kaiser Permanente Northern California, a large integrated health care delivery system in the United States. The averages (and ranges) of ADR for quintiles 1 through 5 were 15.32% (7.35%-19.05%), 21.27% (19.06%-23.85%), 25.61% (23.86%-28.40%), 30.89% (28.41%-33.50%) and 38.66% (33.51%-52.51%), respectively.

[b] 95% Confidence intervals were derived by multiway probabilistic sensitivity analysis.

[c] Patients with adenomas detected had surveillance colonoscopies 3 years after the detection of at least 1 large adenoma or at least 3 adenomas of any size, and 5 years after the detection of at least 3 adenomas with a diameter of less than 10 mm. In case of a negative surveillance colonoscopy, the next interval was 5 or 10 years, depending on whether the length of the preceding interval was 3 or 5 years. Surveillance was continued until death or diagnosis of cancer.

[d] For the simulated effect of fatal perforations on life-years lost, we assumed immediate death.

[e] Besides resources for endoscopy and endoscopy-related complications, screening colonoscopy also influenced the modeled resources for cancer care. Higher ADRs were associated in the model with a lower use of these resources, because of lower associated cancer incidence.

[f] Net screening costs were derived by comparing the estimated total medical costs in case of screening (screening and cancer treatment costs) with the total medical costs in case of no screening. Minor inconsistencies in the resulting net costs are due to rounding.

potential mortality benefit derived from screening (5 weeks per patient). Our estimates of the lifetime disease risk without discounting were consistent with the 4.5% reported risk in the Surveillance Epidemiology and End Results program (eTable 2 in the Supplement).[1]

Screening colonoscopy is considered cost-effective for preventing colorectal cancer through adenoma detection and removal.[12,37] However, it has been suggested that incentivizing higher adenoma detection, for example through value-based purchasing programs,[38] could lead to unacceptably higher cost because of more frequent surveillance in patients with low-risk adenomas.[11] Our model suggests that higher detection rates are associated with only a moderately higher total number of colonoscopies. Although the average surveillance patient in the modeling analysis received about twice as many procedures as a patient without detected adenomas, the additional proportion of patients undergoing surveillance with higher detection rates was limited to a maximum of 17%. By evaluating the costs for screening, surveillance, screening-associated complications and cancer care, our model suggested that ADR is not associated with higher overall costs.

Another theoretical disadvantage of higher ADRs is a higher risk of complications due to more colonoscopies and

polypectomies. The model suggested that for every 5-point higher ADR, the lifetime complication risk is on average 10% higher. The corresponding absolute risk difference of 0.6 per 1000 was counterbalanced in the model by a 3.0 per 1000 lower risk of colorectal cancer and a 0.7 per 1000 lower risk of disease-related mortality (eTable 1 in the Supplement). Our model included mild gastrointestinal symptoms such as nausea or abdominal pain and rare fatal complications. The model's complication rates are somewhat lower than those presented by other studies[33] because we adjusted our estimates for the risk of similar events in the group unexposed to colonoscopy.[22]

The model predicted all colorectal cancer outcomes to be lower for every higher quintile of adenoma detection. These predictions closely replicated the observed interval cancer incidence in the lower 4 quintiles but underestimated adenoma detection and interval cancer incidence for the highest quintile (eFigures 7 and 8 in the Supplement). Although this suggests more uncertainty for the associations beyond approximately 30% (quintile 4 average), in a much larger sample of colonoscopies for all indications from the same data source, a plateau in outcome differences across quintiles was not observed.[10]

This study has some other potential limitations. First, we confined the ADR estimates and analyses to screening colonoscopies. This decreased the number of interval cancers and therefore the precision. However, sensitivity analyses indicated that this did not have a strong effect on long-term model projections (eFigure 7B in the Supplement). Second, colorectal adenomas and cancer risk without screening were modeled using more than 10-year-old data. Uncertainty in corresponding model parameters was assessed with probabilistic sensitivity analysis. Third, our findings for the average association between ADR and patient outcomes do not necessarily mean that modifying ADR alone in individual physicians would lead to fewer interval cancers for their patients, given that modeling cannot prove causal relationships. Fourth, our estimates assumed adherence to screening and surveillance guidelines and that patients received colonoscopies from physicians with similar ADRs throughout their lifetimes. Finally, our cost estimates used Medicare rates and co-payments without supplemental anesthesia costs, and thus may not represent true societal screening costs.[39] We also assumed that there was no overuse of surveillance or screening.[40] However, sensitivity analyses suggested that these surveillance and cost-related factors may not have a large net effect (Figure and eTable 1 in the Supplement).

Conclusions

In this microsimulation modeling study, higher adenoma detection rates in screening colonoscopy were associated with lower lifetime risks of colorectal cancer and colorectal cancer mortality without being associated with higher overall costs. Future research is needed to assess why adenoma detection rates vary and whether increasing adenoma detection would be associated with improved patient outcomes.

ARTICLE INFORMATION

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