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Incremental Benefits of Screening Colonoscopy over Sigmoidoscopy in Average-risk Populations: a model-driven analysis

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Abstract

Purpose—Screening colonoscopy and flexible sigmoidoscopy (FSG) reduce the risk of colorectal cancer (CRC), but the magnitude and duration of protection, particularly against right-sided cancer, remain uncertain. We computed the incremental benefit of colonoscopy over FSG using a validated mathematical model, which reflects colorectal neoplasia growth characteristics while allowing uncertainty in endoscopic detection and removal of adenomas.

Methods—We calibrated models of CRC incidence within a multistage clonal expansion framework to data from: (i) San Francisco-Oakland SEER registry (reference population); and (ii) FSG long-term follow up data from 50,757 individuals after a negative FSG in the Kaiser Permanente system. We compared the residual CRC risks after FSG with full-length colonoscopy.

Results—Our model mirrors trial data with 10-year CRC risk reductions after FSG screening at age 50 years of approximately one third; the optimal age for a ‘once-only’ FSG exam was between ages 50 to 60 years; and the greater benefit was for men compared with women. There were considerable incremental gains in reduction of CRC risk by colonoscopy compared with FSG with the greatest benefit for screening colonoscopy at age 50 years. These results held up against lowering the right-sided adenoma detection sensitivity by 30%, as well as reducing the curative efficacy of polypectomy throughout the colon.

Conclusions—Mathematical modeling of CRC screening, which takes account of important aspects of tumor biology, demonstrates superior risk reductions by colonoscopy over FSG. Our

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predictions provide further rationale for recommending screening colonoscopy in average-risk populations before the age of 60.

Keywords

colorectal cancer screening; flexible sigmoidoscopy; colonoscopy; mathematical modelling

Introduction

While colorectal cancer (CRC) incidence has been declining in the US for over two decades [1], incidence rates continue to increase in many other western populations [2]. Screening for colorectal neoplasia is an effective strategy to protect against CRC [3]. For average-risk populations, data from randomized controlled trials with greater than 10 year follow-up show that screening with flexible sigmoidoscopy (FSG) reduces the incidence of CRC by approximately a third (based on per protocol analyses) [4,5], and that protection is predominantly through reductions in left-sided cancers. Theoretically, colonoscopy should result in an additional risk reduction in CRC incidence compared with FSG, because of added protection against right-sided cancers. However, several population-based studies question this enhanced effectiveness, either showing no protective effect of colonoscopy on right-sided cancer incidence [6–8] and mortality [9]; only modest risk reduction in right-sided cancer incidence [10] and mortality [11,10]; or reporting even higher incidence rates of rightsided cancer compared with the general population [12]. Yet, colonoscopy is widely practiced and endorsed by many clinical guidelines [13–17]. The apparent reduced efficacy of colonoscopy to protect against right-sided cancers may reflect missed lesions or differential tumor biology (e.g., more rapid progression of right-sided neoplasia). Moreover, it remains unclear what the optimal screening interval is after a negative colonoscopy – many guidelines recommend up to 10 years [13–17] - but recent studies suggest that longer intervals may be appropriate without loss in cancer protection [18,19].

Long-term outcomes from large randomized trials are required to address the above uncertainties. However, waiting for the results from screening trials is not practical [20]; two such trials are ongoing, but the results will not be available until 2021 and 2026 (<http://www.clinicaltrials.gov>; identifiers NCT00906997 and NCT00883792, respectively). In the absence of these data, here, we use a validated mathematical screening model for colorectal neoplasia that explicitly allows for age-, sex- and sitespecific differences in adenoma initiation and growth [21,22].

Methods

Study rationale and design overview

To assess screening efficacy of FSG versus colonoscopy, we calibrated a biology-driven multistage clonal expansion model for CRC (see Figure S1) to incidence data from: (i) San Francisco-Oakland SEER (SEER-SFO) registry as reference population; and (ii) data from 50,757 individuals followed-up after negative FSG in the Kaiser Permanente system. The modeling context is illustrated in Figure 1. The percentage reduction in CRC incidence was the difference in the estimated CRC incidence between a screened (FSG or colonoscopy)

and an unscreened reference population. We additionally estimated the reduction in CRC risk by counterfactual colonoscopy screening among individuals who had a negative FSG screening outcome.

Data sources

Using SEER-SFO (1975–2008) as the reference population [23], we obtained the CRC incidence stratified by anatomic site, age, sex, and year of diagnosis. We used the International Classification of Diseases, 10th Revision (ICD-10) codes for cancer site classification for proximal colon (C18.0-Cecum, C18.1-Appendix, C18.2-Ascending colon, C18.3-Hepatic flexure, C18.4-Transverse colon, and C18.5-Splenic flexure), distal colon (C18.6-Descending colon, and C18.7-Sigmoid colon), and rectum (C19.9-Rectosigmoid junction, and C20.9-Rectum). For descriptive purposes, we used the terms ‘right-sided’ as equivalent to proximal colon, and ‘left-sided’ as equivalent to distal colon plus rectum. FSG screening data were obtained from the Colorectal Cancer Prevention (CoCaP) program of Kaiser Permanente in Northern California (KP), which offered FSG to members aged 50 years or older during the 1990s. The demographics of the KP cohort are broadly comparable with those for SEER-SFO registry. Our analysis was restricted to a subpopulation of the KP cohort who underwent FSG between 1994 and 1996, had negative screening results for polyps and CRC (KP negative-FSG cohort), as described elsewhere [24], and subsequently followed for over 10 years. Data collected included demographic information, age at FSG, FSG insertion length, and information on CRC incidence (age at diagnosis, anatomical location). We excluded subjects who had prior endoscopic examinations or were missing information on FSG insertion length [25]. The final dataset consists of 24,627 men and 26,130 women. During follow-up, CRC was diagnosed in 137 men and 144 women. The detailed baseline characteristics, including FSG insertion lengths, are provided in Table S1.

The MSCE-CRC model

Our analysis is based on a cell level multistage model of carcinogenesis in colon and rectum, which allows for the sequential random accumulation of a specific number of mutations (or epigenetic events) before the initiation of a premalignant lesion (here the adenoma) – referred to as the multistage stochastic clonal expansion model (MSCE-CRC) [21,22]. A hallmark of this model is that adenoma initiation requires two rate-limiting mutational events before a stem cell is free to expand clonally (Figure S1). Mathematically, the clonal expansions representing adenoma growth follow stochastic birth-death-mutation processes and therefore include natural size fluctuations that can lead to temporary regressions or ultimate extinctions of some of the adenoma. The model parameters represent the number of susceptible stem cells (X), the mutation rates of the first and second hits at a tumor suppressor gene locus (μ_0 and μ_1), the adenoma cell division rate (α), the adenoma cell death or differentiation rate (β), and the rate at which an adenoma cell gives rise to a clinical cancer (μ_2) [21,26].

Scaling method

The MSCE-CRC model was first calibrated to the observed incidence of proximal colon cancers in the KP negative-FSG cohort (details in supplemental note). Although only the distal colon and rectum were examined by FSG screening in the KP negative-FSG cohort,

we found this cohort at a significantly lower risk for proximal colon cancer (see Results) compared with the SEER-SFO population suggesting selection of low-risk individuals among the screened. This could either be due to the presence of natural heterogeneity in genetic or environmental risk factors that exert similar biological effects in distal and proximal colon, or simply be due to a healthy cohort effect of individuals enrolled in the KP health care system. In either case, the effects modifying CRC risk in left- and right-sided colon will likely be correlated. Specifically, we assumed that the ratios between biological parameters for adenoma initiation, growth (promotion), and progression to cancer in the right-sided and left-sided colon are preserved across cohorts and, by extension, across low- and high-risk individuals. Given this assumption, the potential selection of individuals at low risk for adenoma formation due to genetic/environmental risk factors in this negative-outcome FSG cohort implies a similar low risk for the entire colorectum. Accordingly, we derived left-sided adenoma growth parameters for the negative-outcome FSG cohort using the estimated right-sided parameters from this cohort and ‘scaling’ them up or down using the corresponding left-to-right ratios that we obtained from the SEER-SFO analyses (Figure 1 and Table S2 and S3).

Negative-FSG cohort micro-simulation

We modelled mathematical expressions for the size distribution of screen-detectable premalignant lesions, conditional on no prior detection of cancer as previously described [27]. Biological (i.e. cell level) modeling of adenomas requires knowledge of the relationship between tumor size (in terms of the number of tumor cells) and caliper size of the tumor. For our model calibration, we chose a diameter $d = 1$ mm as the threshold for adenoma detection with a size-dependent sensitivity of 75% for $1 \leq d < 5$ mm, 85% for $5 \leq d < 10$ mm, and 95% for $d \geq 10$ mm [28] and simulated adenoma number and size as described previously [27]. The corresponding detection threshold in terms of the number of stem cells was estimated by comparing the cumulative CRC incidence among these simulated individuals to mimic the KP negative-FSG cohort and the observed cumulative incidence in the same cohort. To address the loss of FSG efficacy due to incomplete scope insertion, we analyzed CRC incidence separately by distal sub-sites (i.e., descending colon, sigmoid colon, and rectum) (details in supplemental note).

Risk prediction of CRC after screening

Our primary outcome measure was the CRC incidence rate per 100,000 at 5-year intervals after screening. Using the SEER-SFO model, we simulated 100,000 individuals to explore three scenarios: 1) no screening; 2) FSG screening adjusted for limited scope insertion; and 3) full length colonoscopy. For FSG screening, a random scope insertion length was drawn from the insertion length distribution observed in the KP cohort. If a simulated individual had a positive FSG outcome (with detection of an adenoma), we assume the occurrence of an immediate follow-up colonoscopy independently of adenoma size. For the full-length colonoscopy scenario, FSG does not occur as an initial test. We compared the results assuming complete (100%) resection of detected adenomas with those generated assuming incomplete (70%) resection of an adenoma mass. The model treats missed adenomas and adenomas too small for endoscopic detection (<1 mm) as left in-situ, allowing them to regress or grow and potentially transform into CRC at a later time. In addition, we assumed

that i) both FSG and colonoscopy have the same sensitivity for adenoma detection in the distal colon and rectum; and ii) the sensitivity of a colonoscopy for adenoma detection is the same across all tumor sites. This represents a ‘best case’ scenario by reflecting recent advances in high-resolution video-endoscopy and increased awareness of the neoplastic potential of sessile serrated adenomas (SSAs) which reflect recent improvements in the adenoma detection rates in proximal colon [Hetzl et al., 2010]. Nonetheless, to explore the potential impact of a much poorer detection in proximal colon due to a higher prevalence of flat or sessile adenomas, we aggressively reduced the detection sensitivity in proximal colon by 30 percent in a separate sensitivity analysis even though the majority of adenomas in proximal colon present as traditional adenomas.

Counterfactual colonoscopy scenario analysis among individuals with negative FSG

A separate simulation study was performed to assess the incremental benefits of counterfactual colonoscopy on CRC risk among those individuals who had a negative FSG screening outcome. Using the SEER-SFO model, we simulated 100,000 individuals to explore two screening scenarios: 1) FSG screening adjusted for limited scope insertion; and 2) full length counterfactual colonoscopy. Here we only considered individuals who had a negative FSG outcome (with no detected adenomas), which were modeled using a random scope insertion length drawn from the observed insertion length distribution. For the counterfactual colonoscopy, we also examined (*in-silico*) the parts of the colon which were not covered by the simulated (limited insertion length) FSG exam, and all detected adenomas were assumed to be either completely removed or partially removed upon detection, as described in the previous section.

Results

Model calibrations

The estimated parameters of the MSCE-CRC models from fitting the CRC incidence in SEER-SFO by sub-site are shown in the Supplement (Table S2 and S3). Consistent with our previous findings [21,22], there were no clear trends by birth cohort, but we found significant calendar year (period) trends that likely reflect the incidence-reducing effects of interventions associated with colorectal screening in the US. We adjusted for screening effects by calendar year using the Age-Period-Cohort approach [29–32] so that the estimated age-related model parameters for the SEER-SFO approximately represent the age effects on cancer incidence in an unscreened population. Again, as in previous reports for other populations [22], we found that, in general, the adenoma initiation rates were higher for the right-sided than the left-sided, while the estimated adenoma growth rates were lower in the right-sided than in the left-sided colon. The adenoma initiation rates were higher in men than women, but the adenoma growth rates were lower in men than women for all sub-sites. The combined effect of these (sex-specific) differences in tumor initiation and growth rates produces fewer but larger adenomas in proximal colon for women compared with men, and suggests that older women might benefit from colonoscopy more than older men (Table 2).

The KP negative-FSG cohort parameters are shown in Tables S2 and S3. In contrast with the SEER-SFO analyses, we made no adjustments for secular trends because the KP cohort was

essentially unscreened prior to the baseline (first) FSG. The likelihood-based analyses of proximal cancer indicated a significantly reduced risk in the KP negative-FSG cohort compared with SEER-SFO (men, $p = 0.024$; women, $p = 0.003$). As described above, we fitted the right-sided models directly to the KP negative-FSG cohort, while the left-sided parameters are based on scaling the right-sided estimates using the left-to-right ratios from the SEER-SFO analyses (Figure 1).

Predicted incidence in the KP negative-FSG cohort

The top panels in Figure 2 show that the predicted incidence rates by sub-site and sex in the KP negative-FSG cohort matches the observed data well. The predicted incidence rates for proximal cancer in the SEER-SFO were significantly higher than those in the KP negative-FSG. For distal (middle panels) and rectal (bottom panels) cancers, using the estimated detection thresholds, our models described well the observed cumulative incidences of distal cancer (descending and sigmoid colon combined) and rectal cancer. As expected, the predicted incidence of distal and rectal cancers using the SEER-SFO estimates were considerably higher than those in the KP negative-FSG cohort, suggesting a significantly lower CRC risk after a negative FSG.

Long-term CRC risk reductions

We quantified the model predictions in terms of an incremental benefit from improved screening for colorectal neoplasia. Table 1 shows the comparative numbers of CRC cases per 100,000 and percent reductions for three different screening ages (50, 60 and 70) for the three scenarios: no screening; FSG; full colonoscopy. Main findings: 1) The FSG model mirrored trial data [4,5] with 10-year risk reductions after FSG at age 50 years of 33.0 percent and 33.6 percent, in men and women, respectively. 2) The optimal age for a 'once-only' FSG exam (which minimizes the lifetime CRC risk) was between ages 50 to 60 years, depending on when the risk is evaluated. 3) There were considerable incremental gains in reduction of CRC risk by colonoscopy compared with FSG. For example, for men, the estimated CRC reductions by age 70 years in those who had colonoscopy screening at age 50 was 65.1 percent compared with 38.3 percent if screened by FSG. 4) The greatest benefit from colonoscopy comes from having the exam at age 50 years. And 5), for almost all screening ages, the incremental benefit of full colonoscopy compared with FSG (i.e., the difference in percentage reduction between FSG and colonoscopy) was greater in women than men. Further results under the assumption of only partial resection of detected adenomas show similar patterns, although the degree of reduction in CRC risk by screening is somewhat smaller (Table S4).

Finally, we conducted additional simulations in which the sensitivity of a colonoscopy to detect proximal adenomas was arbitrarily reduced by 30 percent compared with its sensitivity in distal colon, allowing for the possibility of a higher miss-rate in proximal colon in clinical practice (Table S5). As expected, the incremental benefit of a colonoscopy was somewhat diminished, nonetheless still greater than age-equivalent screening with FSG.

Figure 3 shows age-sex specific CRC incidences for people who had FSG or colonoscopy at age 50 (left), 60 (middle), 70 (right), along with predictions for the unscreened reference

population. The results are based on assuming that the sensitivity of a colonoscopy for adenoma detection is the same across all tumor sites and the detected adenomas were completely removed. Figure 4 provides the relative risk of CRC to an unscreened reference population for two different screening modalities, which shows the long-term CRC risk reduction by FSG and colonoscopy, and the gains of a full-length colonoscopy over FSG, which are more noticeable for women.

Counterfactual colonoscopy scenarios

Another interesting question is to assess the incremental benefit of colonoscopy for individuals who would be negative upon FSG. In other words, what benefit would have been conferred to these individuals if they actually had undergone a colonoscopy instead of FSG? Table 2 shows the percentage reductions of CRC incidence by having counterfactual colonoscopy compared to the risk following a negative FSG. The incremental benefit of a full colonoscopy compared with the risk following a negative FSG was greater in women than men. Again, assuming only partial removal of the detected adenomas, the results show similar patterns but with a lesser degree of reduction in CRC risk by colonoscopy (Table S6). Similarly, results assuming that the sensitivity for proximal adenoma detection was arbitrarily reduced by 30 percent compared with the sensitivity for distal adenoma detection show similar patterns (Table S7).

Discussion

Main findings

Using a validated mathematical model framework for CRC development and screening, and drawing on data from differentially screened populations, the model upheld the hypothesis that colonoscopy has a superior risk reduction compared with FSG in average-risk populations, and that this held true even after accounting for reduced adenoma detection sensitivity in right-sided versus left-sided colon. Through the model's versatility to capture age, sex, and sub-site parameters, there were several secondary findings: (i) the optimal age for a 'once-only' FSG exam was between ages 50 to 60 years; and a greater benefit for men than women; (ii) similarly, for 'once-only' colonoscopy, the greatest benefit was predicted for screening at age 50 years, particularly for women; and (iii) the protective effects of 'once-only' FSG continue past ten years, with colonoscopy extending this protection considerably beyond that point.

Study limitations and strengths

The study has some limitations. First, in common with any mathematical model, our modelling is a simplification of the biological complexity of carcinogenesis and disregards the influence of various modifiers of CRC risk such as obesity [33], physical inactivity [34], alcohol [35], smoking [36], and hormone replacement therapy in women [37]. Second, implicit in the mathematical formulation is the assumption of two rate-limiting events consist with biallelic inactivation of *APC* tumor suppressor gene. Furthermore, tumors may also differ in growth dynamics. For example, tumors with high levels of micro-satellite instability (MSI-H)[38] and/or CpG island methylator phenotype (CIMP)[39] appear to develop through the serrated neoplastic pathway [40], which may require more than two

rate-limiting events for tumor initiation and may differ in growth dynamics. While we do not explicitly model the serrated polyp/hyperplastic polyp pathway, we have previously demonstrated that the exclusion of mucinous carcinoma (that are more closely associated with MSI) from the analysis of CRC incidence data did not significantly alter our risk predictions [22]. Third, adenoma detection sensitivity is a function of both adenoma morphology (flat vs sessile vs pedunculated) and adenoma size distribution. While we model the latter effect through size thresholding, the former is more difficult to assess and is subject to considerable instrument and observer variation [41]. To account for the (potentially) lower detection sensitivity of serrated polyp/hyperplastic polyp in proximal colon due to their more ‘difficult-to-detect’ flat morphology, we also performed a secondary simulation study by reducing the detection sensitivity in proximal colon by 30 percent compared with distal colon. Given recent estimates of adenoma prevalences by subtype[42], we consider this choice sufficiently aggressive because the prevalence of SSAs appears approximately 20-fold lower than that of traditional adenoma in proximal colon (0.9 vs 19.1 per 100 colonoscopies). Four, our modeling implicitly predicts the age-specific adenoma prevalence based on tumor sizes in terms of the number of tumor-forming stem cells which have not yet been fully characterised in the literature.

Our study has several strengths. First, the theory underpinning the mathematical model has been extensively developed [21,43] and validated in clinical scenarios, including evaluation of incidence trends for esophageal adenocarcinomas [44] and pancreatic cancers [26]; exposure-dependent risks for CRC resulting from folic acid supplementation [45]; CRC screening strategies [27]; and CRC incidence trends for the US versus UK populations [22]. Second, the model is versatile in capturing age, sex, and sub-site parameters, allowing a comparison of FSG and colonoscopy by sex, sub-site, across the entire age spectrum, including adjustments for FSG insertion length. Third, we used a novel scaling approach to calibrate our model to the subsequent risk of right- and left-sided cancers after a negative FSG. This allowed us to compare the residual CRC risks after counterfactual colonoscopy screening. Fourth, our modelling eliminates contamination bias from off-protocol colonoscopies, well recognized to occur in both randomized trials and observational studies. This bias attenuates the true effectiveness of the endoscopic screening modality. Finally, by using FSG screening data, we had the opportunity to leverage the incidence of cancers in the unscreened (proximal) part of the colon to address the issue of potential selection based on screening outcome. If the screened population is sufficiently heterogeneous in risk for colorectal neoplasia (viewed across the entire colorectum), we expect to see a lower incidence of right-sided cancers among FSG-negative individuals compared with an unscreened population with a similar risk distribution. Indeed, compared with the SEER-SFO reference population, the KP negative-FSG cohort has a significantly lower risk of cancer in the unscreened (proximal) colon. Alternatively, the lower-than-average risk of right-sided cancers in the KP negative- FSG cohort may also reflect a healthy-cohort effect.

Comparison with other literature

Our results are consistent with several studies. First, our FSG model mirrored the actual FSG screening trial data. The UK Flexi-Scope (40,674 screened) [4] and the Italian SCORE (9,911 screened) [5] trials reported that the total CRC incidence in people (aged 55 to 64

years in both trials) attending screening was reduced by 33 percent and 31 percent, respectively, based on per protocol analyses (which best reflects the FSG scenario in our model). In these trials, the colonoscopy rates resulting directly from findings at FSG occurred in only 5.0% and 8.4%, respectively, such that CRC protection attributable to screening was almost exclusively through left-sided cancer risk reduction. By contrast, for the FSG randomised trial in the Prostate Lung Colorectal and Ovarian study (64,667 screened) [46], the rate of FSG-triggered colonoscopy was 21.9 percent – accordingly, there were risk reductions for both right- and left-sided cancers (report limited to intention-to-treat analyses). Nonetheless, all three trials reported greater benefit for men versus women – and concur with our model. Second, our predicted risk reductions of between 50% to 60% after colonoscopy are consistent with the literature. For instance, analyses from 88,902 participants with over 22 years follow-up from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) [10] have reported reductions in CRC incidence of 56% after negative colonoscopy - although these were not reported based on screening at a specific age.

Clinical implications

Our results support the recommendation of colonoscopy in average-risk populations. However, for a given population, recommendations must include other factors such as individuals' preferences, clinical resources, and cost-benefit considerations. Economical modeling is frequently based on 'blanket' approaches to estimating CRC risk reductions after colonoscopy [47]. Our approach incorporates age- and sex-specific screening input and generates corresponding cancer reduction outputs. Optimal age ranges for either 'once-only' FSG or colonoscopy are between 50 and 60 years – which agree with recommendations by several multi-disciplinary guidelines [13–17]. Our results further suggest that 'once-only' FSG and colonoscopy have long-term benefits with stable protection past 10 years. For FSG, this is consistent with long-term efficacy based on data published a decade ago from the Washington State case-control study [48]. More recently, for colonoscopy, data from the NHS-HPFS cohorts [10] and German populations [49] support suggestions that intervals for CRC screening by colonoscopy could be significantly longer than the commonly recommended 10 years. The key exception is individuals with a strong family history and/or known predispositions to MSI-H and CIMP tumors. Finally, the clinical question remains: 'why do our predictions show protection against proximal cancers after colonoscopy even after considering a significantly lower efficacy of screening for right-sided lesions, while equivalent outputs from population-based studies are inconsistent?' One explanation is that the performance of colonoscopy has improved through greater recognition, for example, of non-polypoidal colorectal neoplasia [42], which was largely unappreciated during the periods of many of the reported population-based studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Scaling method. P=proximal cancer, D=distal cancer (descending colon and sigmoid colon separately), R=rectal cancer. KP distal and rectal cancer model parameters are estimated by taking a KP proximal model parameter and multiplying it by the corresponding SEER-SFO ratio.

Fig. 2.

(a),(b) Proximal colon cancer incidence in the KP negative-FSG cohort (grey line: empirical distribution vs black line: prediction by the MSCE-CRC model). (c)–(f) Empirical distribution vs simulation results (detection thresholds: 10^3 and 10^4 stem cells for distal colon and rectum, respectively); (c), (d) Distal colon cancer incidence (combined descending and sigmoid colon) in the KP negative-FSG cohort, (e), (f) Rectal cancer incidence in the KP-negative FSG cohort. KM curve: Kaplan Meier curve with 95 %

confidence intervals. Black dashed lines: model prediction for cancer incidence in SEER-SFO.

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Fig. 3. Predicted age-specific incidence (hazard) of CRC for people who had screening exam at age 50 (left), 60 (middle), and 70 (right); (1) dotted lines: predicted age-specific incidence of CRC for unscreened reference population. (2) dashed lines: incidence for individuals who had FSG. A positive FSG is assumed to trigger a follow-up colonoscopy. (3) solid lines: incidence for individuals who had ‘once-only’ colonoscopy. Upon detection, adenomas are assumed to be completely resected. These results are based on 100,000 simulated people.

The sensitivity rate for colonoscopy in right-sided colon is assumed the same as the left-sided colon.

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Fig. 4. Relative risk of CRC to unscreened reference population for two screening modality: (1) FSG (dashed lines); (2) Colonoscopy (solid lines). The results are based on 100,000 simulated people who had screening exam at age 50 (left), 60 (middle), and 70 (right). Upon detection, adenomas are assumed to be completely resected. The sensitivity rate for colonoscopy in right-sided colon is assumed the same as the left-sided colon.

Number of CRC cases per 100,000 by endoscopic screening exams; FSG and colonoscopy. The results are based on 100,000 simulated individuals. The sensitivity rate for colonoscopy is assumed to be the same in the right-sided and the left-sided colon.

Table 1

Men		Screening at 50		Screening at 60		Screening at 70	
Age	unscreened	FSG	colono- scopy	FSG	colono- scopy	FSG	colono- scopy
60	796	533	349	-	-	-	-
65	1353	851	505	1051	853	-	-
70	2109	1302	736	1452	1021	-	-
75	3009	1877	1046	1955	1244	2530	2175
80	3926	2518	1415	2505	1500	3047	2376
85	4691	3111	1785	3004	1751	3511	2569
		percentage reductions		Percentage reductions		Percentage reductions	
60		33.0	56.2	-	-	-	-
65		37.1	62.7	22.3	37.0	-	-
70		38.3	65.1	31.2	51.6	-	-
75		37.6	65.2	35.0	58.7	15.9	27.7
80		35.9	64.0	36.2	61.8	22.4	39.5
85		33.7	61.9	36.0	62.7	25.2	45.2
Women		Screening at 50		Screening at 60		Screening at 70	
Age	unscreened	FSG	colono- scopy	FSG	colono- scopy	FSG	colono- scopy
60	755	501	326	-	-	-	-
65	1233	798	456	991	784	-	-
70	1852	1219	645	1375	917	-	-
75	2568	1756	898	1864	1097	2283	1871
80	3290	2348	1198	2401	1307	2793	2015
85	3890	2879	1491	2883	1514	3246	2156

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	percentage reductions		percentage reductions		percentage reductions		percentage reductions	
60	33.6	56.8	-	-	-	-	-	-
65	35.3	63.0	19.6	36.4	-	-	-	-
70	34.2	65.2	25.8	50.5	-	-	-	-
75	31.6	65.0	27.4	57.3	11.1	27.1	11.1	27.1
80	28.6	63.6	27.0	60.3	15.1	38.8	15.1	38.8
85	26.0	61.7	25.9	61.1	16.6	44.6	16.6	44.6

Number of CRC cases per 100,000 by screening scenario; FSG with negative outcome and counterfactual colonoscopy. The results are based on 100,000 simulated individuals. The sensitivity rate for colonoscopy is assumed to be the same in the right-sided and the left-sided colon.

Table 2

Men		Screening at 50		Screening at 60		Screening at 70	
Age		FSG	Colonoscopy	FSG	Colonoscopy	FSG	Colonoscopy
60		527	340	-	-	-	-
65		838	487	1063	860	-	-
70		1279	705	1484	1037	-	-
75		1845	1003	2015	1269	2564	2164
80		2482	1362	2594	1534	3110	2355
85		3076	1728	3116	1790	3595	2540
		percentage reductions		percentage reductions		percentage reductions	
60		35.5		-		-	
65		41.9		19.1		-	
70		44.9		30.1		-	
75		45.6		37.0		15.6	
80		45.1		40.9		24.3	
85		43.8		42.6		29.3	
Women		Screening at 50		Screening at 60		Screening at 70	
Age		FSG	Colonoscopy	FSG	Colonoscopy	FSG	Colonoscopy
60		519	327	-	-	-	-
65		834	463	1009	780	-	-
70		1280	660	1408	910	-	-
75		1843	925	1911	1087	2299	1872
80		2459	1239	2460	1296	2814	2010
85		3007	1543	2950	1502	3267	2146

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	percentage reductions	percentage reductions	percentage reductions	percentage reductions
60	37.0	-	-	-
65	44.5	22.7	-	-
70	48.4	35.4	-	-
75	49.8	43.1	18.6	18.6
80	49.6	47.3	28.6	28.6
85	48.7	49.1	34.3	34.3