Research Article

Cancer Epidemiology, Biomarkers & Prevention

Estimated Mean Sojourn Time Associated with Hemoccult SENSA for Detection of Proximal and Distal Colorectal Cancer

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Abstract

Background: Sojourn time is the length of the preclinical screen-detectable phase, a period when a test can detect asymptomatic disease. Mean sojourn time (MST) is an important factor in determining appropriate screening intervals. Available estimates of MST for colorectal cancer (CRC) are imprecise and are associated with the older Hemoccult II test. This article presents MST estimates associated with the newer Hemoccult SENSA test and describes differences in MST by the location of cancer in the colorectum and age at the time of screening.

Methods: MST was estimated from a cohort of 42,079 patients who underwent Hemoccult SENSA between January 1, 1997 and December 31, 2010. The precision of MST estimates was improved by incorporating information from a meta-analysis of the sensitivity of Hemoccult SENSA into the analytic model.

Results: Estimated MST for cancers in the proximal and distal colorectum, with 95% credible intervals (CrI) in years, were: 3.86 (1.55–6.91) and 3.35 (2.11–4.93) among 45- to 54-year olds; 3.78 (2.18–5.77) and 2.24 (1.48–3.17) among 55- to 64-year olds; and 2.70 (1.41–4.31) and 2.10 (1.34–3.04) among 65- to 74-year olds.

Conclusions: MST associated with Hemoccult SENSA was longer for CRC in the proximal versus distal colon. We found no evidence that MST increases with age and some evidence that it may decrease.

Impact: These results add new information about the natural history of CRC and information about the performance of Hemoccult SENSA. *Cancer Epidemiol Biomarkers Prev; 21(10); 1722–30. ©2012 AACR.*

Introduction

The effectiveness of screening tests depends on test sensitivity, sojourn time, and treatment effectiveness. While much is known about the accuracy of colorectal cancer (CRC) screening tests (1) and treatment effectiveness (2, 3), relatively little is known about its mean sojourn time (MST). Sojourn time is the duration of the preclinical disease state that begins when asymptomatic CRC can be detected by a screening test and ends with clinical detection, that is, when a patient presents with symptoms.

Cohort studies that follow individuals after a negative screening test can be used to jointly estimate test sensitivity and MST. Several studies have estimated sensitivity and MST for Hemoccult II, an older fecal occult blood test (FOBT) (4–9). Unlike accuracy studies, which are cross-sectional and require a reference standard assessment for all participants, cohort studies rely on follow-up data combined with additional model assumptions to estimate sojourn time. Prior studies that jointly estimated MST and sensitivity were based on the Hemoccult II test, and resulting MST estimates were imprecise.

We provide updated estimates of MST associated with Hemoccult SENSA (10), the current standard for high-sensitivity guaiac-based FOBT, and investigate differences in MST by the location of cancer in the colorectum and age at the time of screening. We jointly model sensitivity and MST using data from a cohort of individuals, incorporating information from a meta-analysis of the sensitivity of Hemoccult SENSA to improve the precision of estimates.

Materials and Methods

Meta-analysis of FOBT accuracy studies

We searched Web of Science (11) and Academic Search Complete (12) to identify articles describing the accuracy of Hemoccult SENSA, using combinations of the following terms: "Hemoccult," "colorectal," "sensitivity," "screening," "FOBT," and "SENSA." Because test accuracy balances sensitivity and specificity resulting in correlation between these measures, articles were included in analyses if they focused on a population at average risk for CRC and described the number of true positive outcomes (TP, positive test among individuals with CRC); false positive outcomes (FP, positive test among individuals without CRC); false negative outcomes (FN, negative test

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among individuals with CRC); and true negative outcomes (TN, negative test among individuals without CRC). When articles reported findings from overlapping cohorts, only the most recent study was included. From each article, we recorded first author, year of publication, study period, description of population, study design, reference standard used to determine CRC status, and test outcomes (TP, FP, FN, and TN). We calculated sensitivity and specificity using: sensitivity = TP/(TP + FN), specificity = TN/(FP + TN).

Statistical analysis

We found that sensitivity and specificity were essentially uncorrelated across studies: sensitivity varied widely, whereas specificity was nearly constant. Thus, we summarized sensitivity and specificity separately (13), and our analyses focused on sensitivity. We combined information across studies using a random effects model (14) to allow for between-study heterogeneity in sensitivity. Analyses used MetaAnalyst software (15), and estimates are reported with 95% confidence intervals (CI).

Joint estimation of sensitivity and MST

Analyses use data from a retrospective cohort of individuals, ages 45 to 74 years, who had at least one Hemoccult SENSA FOBT between January 1, 1997 and December 31, 2010 while being members of Group Health Cooperative, a large health care system in Washington State. During this period, Hemoccult SENSA was used for all FOBT at Group Health. However, overall CRC screening guidelines changed over the study period. In 1997, the screening guideline for average-risk members was FOBT (using Hemoccult SENSA) every 2 years plus flexible sigmoidoscopy every 10 years. Guidelines added colonoscopy as a screening modality in 2001, when Medicare began coverage for screening colonoscopy (16, 17). In 2004, guidelines were modified to recommend shorter FOBT screening intervals, with FOBT every 1 to 2 years. In 2006, FOBT screening intervals were shortened again to every year. Throughout the study period, all patients with a positive FOBT were recommended for referral to colonoscopy.

Individuals enter the cohort at the time of their first known (index) FOBT. We excluded individuals with less than 6 months of follow-up, unless they were diagnosed with CRC within 6 months of their index FOBT. We also excluded individuals who had lower endoscopy (flexible sigmoidoscopy or colonoscopy) before their FOBT, because this reduces the risk of developing CRC (18). We excluded individuals with a total bowel resection or any diagnosis of cancer other than nonmelanoma skin cancer before their index FOBT because these individuals are ineligible for routine CRC screening. CRC diagnoses were identified using Surveillance Epidemiology and End Results (SEER) data (19). The location of CRC was coded as proximal (located in the cecum, ascending, or transverse colon) or distal (located in the descending or sigmoid colon, or the rectum). We excluded one CRC with an unspecified location.

Individuals with a positive index FOBT contributed information about screen-detected CRC, defined as CRC diagnosed within 6 months after a positive index FOBT. We treated 17 CRCs diagnosed more than 6 months after a positive index FOBT as FP tests (13 were diagnosed more than a year after screening).

Individuals with a negative index FOBT contributed information about symptom-detected CRC and were followed until the first occurrence of 1 of 5 endpoints: (i) symptom-detected CRC; (ii) next CRC test (FOBT, flexible sigmoidoscopy, colonoscopy, or barium enema); (iii) death or disenrollment from the health plan; (iv) end of screening eligibility because of colonic resection or diagnosis with any non-CRC other than nonmelanoma skin cancer; or (v) end of study period. Symptom-detected CRC is an observed event, whereas other endpoints are censoring events. We assume that CRC is symptom-detected if the diagnosis is made without evidence of a prior FOBT (excluding the index test), flexible sigmoidoscopy, or barium enema. This assumes that FOBT, flexible sigmoidoscopy, and barium enema were used for screening. We make the simplifying assumption that all colonoscopy during this period was diagnostic (used to evaluate symptoms), an assumption we explore in sensitivity analyses. Thus, we included CRC diagnosed within 6 months of the first colonoscopy as symptom-detected. Six individuals with CRC diagnosed more than 6 months after a colonoscopy could not be categorized as interval cancers; their follow-up time was censored at the time of their first colonoscopy.

Statistical model

We use information from screen-detected cancers and symptom-detected cancers that arise during follow-up after a negative FOBT to estimate sensitivity and MST for 3 strata based on age (in years) at the time of the index FOBT: 45 to 54, 55 to 64, and 65 to 74. Within each strata, let n denote the number of people who had an index FOBT at age T and let S denote the sensitivity of FOBT to detect preclinical CRC when present. Among these n individuals, c_P proximal CRCs are screen-detected and c_D distal CRCs are screen-detected. We assume that $(c_P, c_D, n - c_P - c_D)$ follows a multinomial distribution. Let L indicate the location of cancer with $L = P$ for proximal CRC and $L = D$ for distal CRC. The probability of detecting CRC in location L at the time of screening at age T is given by $S \times P(\lambda_L, J_L, T)$, in which $P(\lambda_L, J_L, T)$, the probability of preclinical CRC at the age T, is a function of the location-specific incidence rate of preclinical CRC (J_L) and the location-specific incidence rate of clinical CRC (λ_L).

We estimate $P(\lambda_L, J_L, T)$ using a time-homogeneous Markov model (20) that describes transitions through 3 disease states: disease free, preclinical disease, and clinical disease. Transition time between these states is modeled with an exponential distribution (e.g., time from preclinical to clinical CRC has probability density function $f(s) = \lambda_L \exp(-\lambda_L s)$ so that MST is equal to $1/\lambda_L$; refs. 4–6, 8, 9, 21). Among asymptomatic individuals, the probability

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of being in the preclinical state at age T is equal to the probability of transitioning into the preclinical disease state by age T divided by the probability of either remaining in the disease-free state or transitioning into the preclinical state by age T:

$$P(\lambda_L, J_L, T) = \frac{J_L\left(e^{-\lambda_L T} - e^{-J_L T}\right)/(J_L - \lambda_L)}{e^{-J_L T} + J_L(e^{-\lambda_L T} - e^{-J_L T})/(J_L - \lambda_L)} \quad (1)$$

We treat unobservable preclinical CRC incidence rates J_P and J_D as known constants approximated by the observed clinical incidence from 1975 to 1979 SEER data (5, 6, 19, 21, 22), using this time period because it precedes the diffusion of CRC screening and so reflects incidence in an unscreened population. We assumed that preclinical disease incidence rates were constant within age strata, setting J_P equal to 1.08, 3.08, and 7.92 per 10,000, for ages 45 to 54, 55 to 64, and 65 to 74 years, and setting J_D equal to 2.95, 7.96, and 15.6 per 10,000 for ages 45 to 54, 55 to 64, and 65 to 74 years.

We approximate the age at screening, T, with the strata midpoint (e.g., we use $T = 50$ for 45–54-year-old individuals). This approximation is needed to calculate equation (1). This assumption had no impact on estimates because within each age strata and for plausible values of λ and J, $P(\lambda,J,T)$ depends on λ but varies little with T. This can be seen by reexpressing equation (1) as $P(\lambda_L, J_L, T) = 1 - (J_L - \lambda_L)/(J_L \exp[(J_L - \lambda_L)T] - \lambda_L)$. Developing preclinical disease is rare, but once preclinical disease has developed clinical disease is not rare. Therefore, for both proximal and distal locations, the overall preclinical disease incidence, J_L, is much smaller than clinical disease incidence among individuals with preclinical disease, λ_L so equation (1) is dominated by $(J_L - \lambda_L)/\lambda_L$.

Let t indicate follow-up time. The index FOBT occurs at time $t = 0$. During the tth follow-up year, $(t - 1, t]$ years since the negative index FOBT, we observe x_{Pt} symptom-detected proximal CRCs and x_{Dt} symptom-detected distal CRCs among y_t person-years at risk. Individuals are at risk in the tth follow-up year if they were followed at least t years or were diagnosed with CRC during the tth follow-up year. For $t = 1, 2, \ldots, k$, we assume that $(x_{Pt}, x_{Dt}, y_t - x_{Pt} - x_{Dt})$ follows a multinomial distribution. The probability of symptom-detected CRC in location L is equal to $I(t,S, J_L,\lambda_L,c_L)/y_t$, in which the expected number of symptom-detected CRCs in the tth follow-up year is given by:

$$\begin{aligned} &I(t,S,J_L,\lambda_L,c_L) \\ &= y_t J_L \int_0^{t-0.5} f(s)ds + \frac{c_L(1-S)}{S}\left[1 - \int_0^{t-0.5} f(s)ds\right] \\ &= y_t J_L[1 - \exp(-\lambda_L(t-0.5))] + \frac{c_L(1-S)}{S}\exp(-\lambda_L(t-0.5)) \end{aligned}$$

Symptom-detected cancers are a mixture of preclinical cancers present but missed at the time of the index screening (FN tests) and new cancers that developed after the index screening (TN tests). We assume that individuals with symptom-detected CRC in the tth follow-up year entered the clinical disease state at the midpoint of the tth follow-up year. The expected number of symptom-detected CRCs in follow-up year t that were missed by screening is the product of the expected number of preclinical CRCs missed by screening ($c_L(1 - S)/S$), and the probability that their sojourn time is greater than or equal to $t - 0.5$, assuming that these individuals entered the preclinical disease state before or at the time of the index screening test. The expected number of newly developed CRCs that are symptom-detected in follow-up year t is the product of the expected number of new preclinical cancers ($y_t J_L$) and the probability that their sojourn time is less than or equal to $t - 0.5$, assuming that these individuals entered the preclinical disease state after the time of the index screening test.

For each age strata, the joint likelihood is given by the product, L_1L_2. L_1 is associated with screen-detected CRC:

$$\begin{aligned} L_1 = &\left(\frac{n!}{c_P!c_D!(n - c_P - c_D)!}\right)(S \times P(\lambda_P, J_P, T))^{c_P} \\ &\times (S \times P(\lambda_D, J_D, T))^{c_D}(1 - S \times P(\lambda_D, J_D, T) \\ &- S \times P(\lambda_D, J_D, T))^{(n - c_P - c_D)} \end{aligned}$$

L_2 is associated with symptom-detected CRC during follow-up:

$$\begin{aligned} L_2 = \prod_{t=1}^{k} &\left\{ \left(\frac{y_t!}{x_{Pt}!x_{Dt}!(y_t - x_{Pt} - x_{Dt})!}\right) \right. \\ &\times \left(\frac{I(t, S, J_P, \lambda_P, c_P)}{y_t}\right)^{x_{Pt}} \\ &\times \left(\frac{I(t, S, J_D, \lambda_D, c_D))}{y_t}\right)^{x_{Dt}} \\ &\left. \times \left(1 - \frac{I(t, S, J_P, \lambda_P, c_P)}{y_t} - \frac{I(t, S, J_D, \lambda_D, c_D))}{y_t}\right)^{y_t - x_{Pt} - x_{Dt}} \right. \end{aligned}$$

We use a Bayesian model, specifying prior distributions for $1/\lambda_P$, $1/\lambda_D$ and S. We assume S has a Normal prior based on our meta-analysis of FOBT sensitivity. Because we lacked information about MST, we assumed a Uniform (0.05, 10) prior distribution for MST associated with both proximal ($1/\lambda_P$) and distal ($1/\lambda_D$) CRC.

We jointly estimated MST and sensitivity using Gibbs sampling, implemented using WinBUGs software (23). We assessed convergence using the method of Gelman and Rubin (24), based on 5 chains started at widely dispersed points in the sample space. Our estimates are based on simulated draws that showed evidence for convergence, with Gelman and Rubin statistics greater than 0.99. We report estimated mean sensitivity and sojourn times with 95% credible intervals (CrI; ref. 25). The bounds of 95% CrI are estimated by the 25th and 75th percentiles of the simulated posterior samples. The 95% CrI is an interval with a 95% probability of containing the

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true parameter value. We used pairwise comparisons to test for differences in MST by age strata and CRC location and present estimated mean differences with posterior probabilities that these differences are greater than 0 to indicate statistical significance (25).

We carried out several sensitivity analyses to explore the impact of model assumptions. We estimated a model that allowed the incidence rate of preclinical cancer, J, to increase over the follow-up period, based on linear interpolation of J at ages 50, 60, and 70 years. We estimated models stratified by the year of index FOBT, using strata based on changes to guideline recommendations: 1997 to 1999, 2000 to 2002, 2003 to 2005, and 2006 to 2010. We also estimated models that treated the 17 patients with CRC detected more than 6 months after a positive index FOBT as TP test results. Finally, we estimated a model that specified a Uniform (0.001,0.999) prior distribution for S.

Results

Meta-analysis of FOBT accuracy studies

Thirty studies met our criteria for review. We excluded 25 studies because of insufficient data to calculate sensitivity and specificity ($n = 17$), their sample represented a population at high risk for CRC ($n = 3$), their study sample overlapped with another included study ($n = 3$), or no primary data were reported (e.g., simulation studies, $n = 2$). Our meta-analysis included 5 studies that estimated both the sensitivity and specificity of Hemoccult SENSA in an average risk population (Table 1; Fig. 1; refs. 26–31). The estimated overall sensitivity was 0.748 (95% CI: 0.630–0.839), which corresponds to a Normal prior distribution for S with mean 0.748 and SD 0.05, truncated to the range from 0.001 to 0.999.

Jointly estimated sensitivity and MST

Our cohort included 42,079 individuals. Overall rates of a positive FOBT were 6% to 7%, approximately half of the patients in our sample were women, and the average age at index screening was about 56 years (Table 2). Among subjects with a negative index FOBT, the average follow-up time was about 3 years (Table 3). The length of follow-up decreased over time, consistent with decreases in recommended screening intervals and a shorter time to the end of the follow-up period. Over time, the percentage of individuals censored because of colonoscopy increased from 6.7% to 10.7% with similar trends across age strata. While the reasons for censoring shifted away from FOBT and toward colonoscopy, patterns of censoring were similar across age strata (data not shown).

We identified 93 screen-detected cancers [29 proximal and 64 distal (13 rectum)] and 52 symptom-detected cancers [32 proximal and 20 distal (4 rectum)]. Estimated sensitivity was stable across age strata (Table 4). MST was longer in the proximal than distal colon (Tables 4 and 5). MST was shorter in older age strata, especially for cancer in the distal colorectum (Tables 4 and 5).

Sensitivity analysis resulted in similar findings. Analyses stratified by year of index FOBT showed no evidence of systematic changes in MST over time. MST estimates based on a model with a Uniform (0.001, 0.999) prior distribution for S were similar to analyses presented but with greater variability. Our results were unaffected by assumptions about patients with CRC detected more than 6 months after a positive index FOBT.

Discussion

Our study is the first to jointly estimate the sensitivity and MST based on the newer, highly sensitive guaiac-

Table 1. Characteristics of studies for average risk populations

Study (Year)	Study period	Population	Study design	Gold standard	TP	FN	FP	TN	Sensitivity	Specificity
Allison (2007) (29)	4/1997–10/1999	Patients, ages 50 to 80 years, at average risk for CRC	Prospective	Colonoscopy for test positive, Flex Sig for test negative, plus 2-year follow-up	9	5	575	5,210	64.3%	90.1%
Allison (1996) (26)	10/1990–10/1991	People at least 50 years old with an average risk of CRC	Prospective	Flex Sig for Hemoccult II SENSA positive, 2-year follow-up	27	7	1,046	6,824	79.4%	86.7%
Ahlquist (2008) (30)	2001–2007	Asymptomatic persons, ages 50 to 80 years, at average risk for CRC	Cross-sectional	Colonoscopy for all participants	12	7	144	3,601	63.2%	96.2%
Rennert (2001) (28)	1992–1997	Asymptomatic patients in Israel, ages 50 to 74 years	Prospective	Full colonoscopy or sigmoidoscopy plus double contrast barium enema for test positive with follow-up with mean time 34.1 months	58	10	977	21,148	85.3%	95.6%
Rozen (1997) (27)	Not stated	97% Consecutive asymptomatic persons and 3% symptomatic patients evaluated for abdominal complaints	Cross-sectional	Colonoscopy for test positive, otherwise flexible sigmoidoscopy	3	2	32	366	60.0%	92.0%

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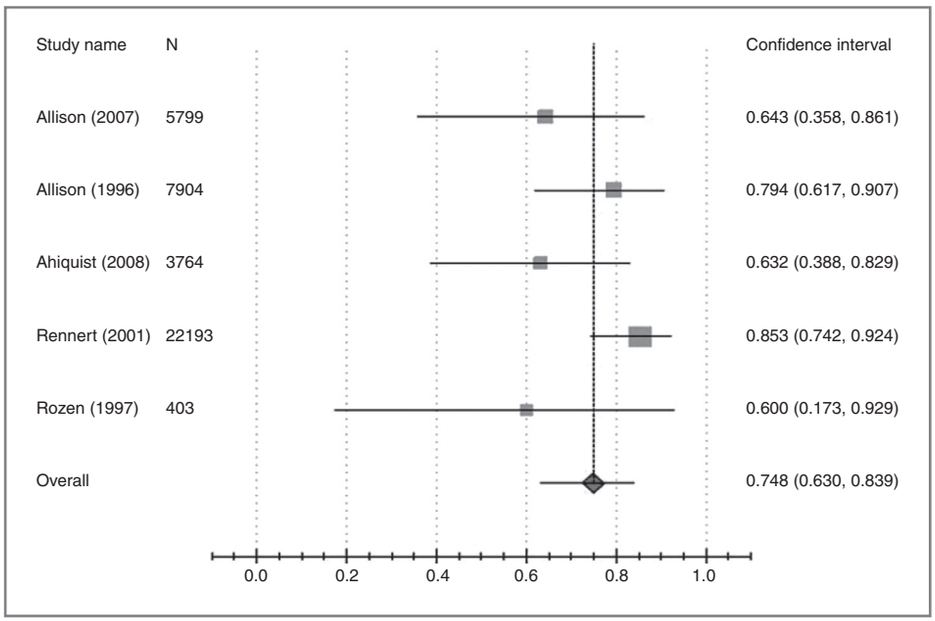

Figure 1. Forest plot of estimated Hemoccult SENSA sensitivity in average risk populations.

based Hemoccult SENSA test, and is the first to estimate MST by both location in the colorectum and age at the time of screening.

We found that MST associated with Hemoccult SENSA was longer for CRC in the proximal versus distal colon. This finding is consistent with the current knowledge of biologic differences in left- and right-sided CRC (32–34). It is well established that there are multiple pathways to CRC, and the frequency of carcinomas arising from these different pathways varies by anatomic location (35). The most common pathway, termed the conventional adenoma–carcinoma pathway, results in carcinomas that tend to exhibit chromosomal instability (CIN) but lack microsatellite instability (MSI; ref. 36). A separate pathway, the "serrated pathway," is associated with carcinomas characterized by a CpG island methylator phenotype (CIMP), MSI, and often *BRAF*-mutation (37–39). The serrated pathway is much more common in the proximal colon than in the distal colon and rectum, as evidenced by the distribution of CIMP-positive carcinomas, with 30% to 32% of proximal colon cancers being CIMP-positive, compared with 3% to 5% of distal colon and rectal carcinomas (40, 41). There is also evidence that cancer exhibiting molecular markers associated with the serrated pathway, specifically MSI (42, 43) and CIMP (44, 45), are associated with better prognosis than cancers without these molecular markers. Therefore, estimated differences in MST for cancers in the proximal and distal colon may reflect differences in pathways leading to cancer. Despite the uncertainty about the time to progression for cancers in the serrated pathway, this may be evidence for a less aggressive disease with longer MST.

We found no evidence that MST increased with age, and some evidence that it may decrease. This may reflect other age-related differences in the characteristics of CRCs.

Our models differed somewhat from earlier approaches. We extended the model proposed by Prevost and colleagues (6) to investigate differences in MST by location, using a multinomial distribution to simultaneously describe the occurrence of proximal and distal CRC. We

Table 2. Characteristics of the cohort

	Year of index FOBT test			
	1997–1999 (n = 13,556)	**2000–2002 (n = 10,209)**	**2003–2005 (n = 7,879)**	**2006–2010 (n = 10,435)**
Positive FOBT, %	6.7	6.3	7.3	7.0
Female, %	53.5	55.3	55.1	54.3
Age, y				
Mean (SD)	57.7 (7.8)	56.1 (7.1)	55.3 (6.5)	56.2 (6.4)
45–54, %	43.4	53.1	56.0	48.8
55–64, %	33.5	31.5	32.8	38.5
65–74, %	23.1	15.4	11.2	12.7

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Table 3. Follow-up information for individuals with a negative FOBT. Individuals with less than 1 year of follow-up contributed information only if diagnosed with CRC within 1 year of a negative FOBT.

	Year of index FOBT test			
	1997–1999 (n = 12,647)	2000–2002 (n = 9,562)	2003–2005 (n = 7,304)	2006–2010 (n = 9,708)
Follow-up time, yrs				
Mean (SD)	3.4 (2.7)	3.2 (2.3)	2.9 (1.7)	1.6 (1.0)
<1, %	10.5	11.8	12.3	32.5
1–<2, %	25.7	24.7	25.1	40.6
2–<3, %	23.4	23.3	23.8	16.8
3–<4, %	13.0	12.5	14.6	6.8
4+, %	27.4	27.7	24.2	3.3
Reason end follow-up, %				
CRC diagnosis	0.2	0.1	0.1	0.1
FOBT, flexible sigmoidoscopy, or barium enema	66.8	60.2	53.6	29.8
Colonoscopy	6.7	11.1	17.8	10.7
Non-CRC cancer or resection	2.8	2.1	1.8	0.9
Disenrollment	20.5	21.7	18.8	9.7
Death	1.2	0.9	0.6	0.2
End of follow-up	1.8	3.9	7.3	48.6

incorporated information from a meta-analysis of the sensitivity of Hemoccult SENSA to increase the precision of our estimates. The resulting Normal prior distribution for sensitivity improved precision but did not drive our findings.

Because both Hemoccult SENSA and Hemoccult II are guaiac-based tests that detect bleeding, we expected that our results would be similar to earlier findings for Hemoccult II. Our MST estimates (ranging from 2.7 to 3.9 years) were longer than previous estimates. The first study to jointly estimate MST and sensitivity estimated a 2.1-year MST (SE = 0.18; ref. 4). A subsequent study (5) estimated sensitivity and MST for cancers in the proximal colon, distal colon, and rectum, and found that the sensitivity was similar for all 3 locations; MSTs varied with location, although estimates were imprecise: estimated MST was 3.5 years (95% CI: 1.6–11.3) for the proximal colon, 6.4 years (95% CI: 3.9–14.8) for the distal colon, and 2.6 years (95% CI: 1.2–11.2) for the rectum. A third study estimated a 2.6-year MST (8).

We found some evidence that MST decreased with age. Previous studies have generally found an increase in MST with age. The first study to examine age differences in MST found that the sensitivity of Hemoccult II decreased with age, whereas MST increased with age, although 95% CrIs associated with these MST estimates were more than 10 years wide (6). An additional analysis of these data reported estimated MST of 3.4 years for 50-year olds and 5.8 years for 60-year olds, although the precision of estimates was not reported (7).

We made several simplifying assumptions when building our models. Sensitivity analysis showed that our results were robust to many assumptions. In particular, while primary analyses restricted the variability of FOBT sensitivity across age groups, analyses that allowed sensitivity to vary across age groups, using a Uniform prior distribution, produced similar findings. The influence of some assumptions was untested. We assumed that FOBT sensitivity was the same for proximal and distal CRC. This is consistent with earlier estimates from joint estimation of MST and sensitivity (5). Additional support for this assumption comes from a 1992 study of individuals with newly diagnosed CRC that found that the sensitivity of Hemoccult II did not vary for proximal and distal CRC

Table 4. Estimated sensitivity and MST, with 95% credible intervals

		Mean sojourn time (MST)	
Index age	Sensitivity	Proximal colon	Distal colorectum
45–54	0.87 (0.80–0.94)	3.86 (1.55–6.91)	3.35 (2.11–4.93)
55–64	0.87 (0.80–0.93)	3.78 (2.18–5.77)	2.24 (1.48–3.17)
65–74	0.82 (0.75–0.90)	2.70 (1.41–4.31)	2.10 (1.34–3.04)

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Table 5. Comparison of MST by site and age group

	Average MST difference	95% Credible interval	Posterior probability[a]
Proximal vs. distal colorectum			
Index age 45–54 yrs	0.51	(−2.33–3.85)	0.61
Index age 55–64 yrs	1.54	(−0.31–3.66)	0.95
Index age 65–74 yrs	0.60	(−1.03–2.40)	0.75
Index age 55–64 vs. 45–54 yrs			
Proximal colon	−0.09	(−3.52–2.99)	0.49
Distal colorectum	−1.11	(−2.89–0.44)	0.08
Index age 65–74 vs. 45–54 yrs			
Proximal colon	−1.16	(−4.47–1.66)	0.23
Distal colorectum	−1.25	(−3.01–0.31)	0.06
Index age 65–74 vs. 55–64 yrs			
Proximal colon	−1.08	(−3.44–1.16)	0.18
Distal colorectum	−0.14	(−1.34–1.08)	0.41

[a]The estimated posterior probability that the difference is greater than 0.

(46). Further support comes from a study, which found that the distribution of cancer across locations in the colorectum was similar for an FOBT-screened group ($n = 100$) and an unscreened group ($n = 1{,}390$; ref. 47).

Our data have 2 important limitations. First, we were unable to distinguish between screening and diagnostic tests. We assumed that FOBT, flexible sigmoidoscopy, and barium enema were used to screen for CRC, and censored individuals at the time of additional tests. Some of these tests may have been conducted in response to symptoms. Resulting misclassification of symptom-detected cancers as screen detected (censored at the time of the examination) would bias our results toward longer MST. We also assumed that all colonoscopy was diagnostic, although the uptake of screening colonoscopy increased over the study period (48–50). Misclassifying cancer detected by screening colonoscopy as symptom-detected would bias our results toward shorter MST. Results from models stratified by year of index FOBT did not show the shortening of MST over time that would be expected with increased screening colonoscopy. Older age groups may also seem to have shorter MST if older individuals were more likely to undergo screening colonoscopy. We did not find evidence of differential rates of colonoscopy across age groups.

Another limitation is the potential for informative censoring. Our estimates are based on differences between the expected and observed numbers of symptom-detected CRC during the follow-up period. Individuals were removed from the risk set when they were retested for CRC, regardless of whether this was for screening or symptom evaluation. If this censoring mechanism differentially removes individuals at higher risk of CRC, then remaining individuals are at lower risk than the overall population, resulting in higher estimates of sensitivity (fewer missed cancers that later become symptomatic) and longer estimates of MST (fewer new cancers that become symptomatic). Estimated age differences could be biased if there was differential censoring of individuals at greater risk for CRC and the degree of differential censoring varied across age strata. We cannot rule out differential selection into screening across age strata, even though we found no evidence for differential censoring.

Finally, while we found evidence of longer MST for proximal CRC, this could reflect differences in the detection accuracy for proximal and distal cancers. If symptomatic proximal cancers are more frequently missed (e.g., because they arise from flat or sessile polyps; ref. 51), this could delay diagnosis and create the appearance that proximal CRC has a longer sojourn time.

Our MST estimates provide support for annual CRC screening with Hemoccult SENSA. Further studies that more fully explore differences in MST by gender, race, and risk factors, such as family history, could provide additional information to guide personalized screening regimens.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: W. Zheng, C.M. Rutter
Development of methodology: W. Zheng, C.M. Rutter
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.M. Rutter
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W. Zheng, C.M. Rutter
Writing, review, and/or revision of the manuscript: W. Zheng, C.M. Rutter
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.M. Rutter
Study supervision: C.M. Rutter

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References

1. Whitlock EP, Lin J, Liles E, Beil T, Fu R, O'Connor E, et al. Screening for colorectal cancer: an updated systematic review. Portland: Oregon Evidence-based Practice Center; 2008. Report No:08-05-05124-EF-1.
2. Aschele C, Bergamo F, Lonardi S. Chemotherapy for operable and advanced colorectal cancer. Cancer Treat Rev 2009 35:509–16.
3. Graham JS, Cassidy J. Adjuvant therapy in colon cancer. Expert Rev Anticancer Ther 2012;12:99–109.
4. Gyrd-Hansen D, Sogaard J, Kronborg O. Analysis of screening data: colorectal cancer. Int J Epidemiol 1997;26:1172–81.
5. Launoy G, Smith TC, Duffy SW, Bouvier V. Colorectal cancer mass-screening: estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. Int J Cancer 1997;73:220–4.
6. Prevost TC, Launoy G, Duffy SW, Chen HH. Estimating sensitivity and sojourn time in screening for colorectal cancer: a comparison of statistical approaches. Am J Epidemiol 1998;148:609–19.
7. Pinsky PF. Estimation and prediction for cancer screening models using deconvolution and smoothing. Biometrics 2001;57:389–95.
8. Jouve JL, Remontet L, Dancourt V, Lejeune C, Benhamiche AM, Faivre J, et al. Estimation of screening test (Hemoccult) sensitivity in colorectal cancer mass screening. Br J Cancer 2001;84:1477–81.
9. Wu D, Erwin D, Rosner GL. Estimating key parameters in FOBT screening for colorectal cancer. Cancer Causes Control 2009;20:41–6.
10. Beckman Coulter Inc; 2012 [cited 2012 Aug 30]. Available from: www.beckmancoulter.com/wsrportal/wsr/diagnostics/clinical-products/rapid-diagnostics/hemoccult-sensa/index.htm
11. Web of Science; 2012 [cited 2012 Aug 30]. Available from: wokinfo.com/products_tools/multidisciplinary/webofscience/
12. Academic Search Complete; 2012 [cited 2012 Aug 30]. Available from: www.ebscohost.com/academic/academic-search-complete
13. Chappell FM, Raab GM, Wardlaw JM. When are summary ROC curves appropriate for diagnostic meta-analyses? Stat Med 2009;28:2653–68.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
15. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 2009;9:80.
16. Shih YC, Zhao L, Elting LS. Does medicare coverage of colonoscopy reduce racial/ethnic disparities in cancer screening among the elderly? Health Aff (Millwood) 2006;25:1153–62.
17. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology 2003;124:544–60.
18. Zauber AG, Winawer SJ, O'Brien M J, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–96.
19. Ries LAG, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK, (eds). SEER cancer statistics review, 1973–1996. National Cancer Institute. Bethesda, MD, 1999.
20. Duffy SW, Chen HH, Tabar L, Day NE. Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. Stat Med 1995;14:1531–43.
21. Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. Biometrics 1984;40:1–14.
22. Paci E, Duffy SW. Modelling the analysis of breast cancer screening programmes: sensitivity, lead time and predictive value in the Florence District Programme (1975–1986). Int J Epidemiol 1991;20:852–8.
23. Thomas A, Spiegelhalter DJ, Gilks WR. BUGS: a program to perform Bayesian inference using Gibbs sampling. In:Bernando JM, Berger JO, Dawid AP, editors. Bayesian statistics 4: proceedings of the fourth Valencia International Meeting. England: Clarendon Press; 1992. p. 837–42.
24. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Stat Sci 1992;7:457–511.
25. Berger JO. Statistical decision theory and Bayesian analysis. 2nd ed. New York: Springer-Verlag; 1985.
26. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155–9.
27. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. Dig Dis Sci 1997;42:2064–71.
28. Rennert G, Rennert HS, Miron E, Peterburg Y. Population colorectal cancer screening with fecal occult blood test. Cancer Epidemiol Biomarkers Prev 2001;10:1165–8.
29. Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007;99:1462–70.
30. Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441–50.
31. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627–37.
32. Protiva P. Colorectal cancer screening pathways. In: Anderson JC, Kahi CJ, editors. Colorectal cancer screening, clinical gastroenterology. New York: Springer Science + Business Media LLC; 2011. p. 1–5.
33. Worthley DL, Leggett BA. Colorectal cancer: molecular features and clinical opportunities. Clin Biochem Rev 2010;31:31–8.
34. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005;23:609–18.
35. Jass JR. Molecular heterogeneity of colorectal cancer: implications for cancer control. Surg Oncol 2007;16(Suppl 1):S7–9.
36. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159–70.
37. Jass JR. Hyperplastic polyps of the colorectum-innocent or guilty? Dis Colon Rectum 2001;44:163–6.
38. Hawkins NJ, Ward RL. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. J Natl Cancer Inst 2001;93:1307–13.
39. Kambara T, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut 2004;53:1137–44.
40. Barault L, Charon-Barra C, Jooste V, de la Vega MF, Martin L, Roignot P, et al. Hypermethylator phenotype in sporadic colon cancer: study on a population-based series of 582 cases. Cancer Res 2008;68:8541–6.
41. Nosho K, Irahara N, Shima K, Kure S, Kirkner GJ, Schernhammer ES, et al. Comprehensive biostatistical analysis of CpG island methylator phenotype in colorectal cancer using a large population-based sample. PLoS ONE 2008;3:e3698.
42. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073–87, e3.
43. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816–9.
44. Ogino S, Nosho K, Kirkner GJ, Kawasaki T, Meyerhardt JA, Loda M, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. Gut 2009;58:90–6.

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45. Min BH, Bae JM, Lee EJ, Yu HS, Kim YH, Chang DK, et al. The CpG island methylator phenotype may confer a survival benefit in patients with stage II or III colorectal carcinomas receiving fluoropyrimidine-based adjuvant chemotherapy. BMC Cancer 2011;11:344.
46. St John DJ, Young GP, McHutchison JG, Deacon MC, Alexeyeff MA. Comparison of the specificity and sensitivity of Hemoccult and Hemo-Quant in screening for colorectal neoplasia. Ann Intern Med 1992; 117:376–82.
47. Harmston C, Hunter J, Wong L. Does the location of screen-detected cancers differ from that seen in the unscreened population? Colorectal Dis 2010;12:324–6.
48. Schenck AP, Peacock SC, Klabunde CN, Lapin P, Coan JF, Brown ML. Trends in colorectal cancer test use in the medicare population, 1998–2005. Am J Prev Med 2009;37:1–7.
49. Holden DJ, Jonas DE, Porterfield DS, Reuland D, Harris R. Systematic review: enhancing the use and quality of colorectal cancer screening. Ann Intern Med 2010;152:668–76.
50. Richardson IC, Rim SH, Plescia M. Vital signs: colorectal cancer screening among adults aged 50–75 years—United States, 2008. MMWR Morb Mortal Wkly Rep 2010;59:808–12.
51. Huang CS, Farraye FA, Yang S, O'Brien MJ. The clinical significance of serrated polyps. Am J Gastroenterol 2011;106:229–40.

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