CLINICAL–ALIMENTARY TRACT

Interval Fecal Immunochemical Testing in a Colonoscopic Surveillance Program Speeds Detection of Colorectal Neoplasia

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BACKGROUND & AIMS: Rapidly progressing or missed lesions can reduce the effectiveness of colonoscopy-based colorectal cancer surveillance programs. We investigated whether giving fecal immunochemical tests (FITs) for hemoglobin between surveillance colonoscopies resulted in earlier detection of neoplasia. **METHODS:** The study included 1736 patients with a family history or past neoplasia; they received at least 2 colonoscopy examinations and were followed for a total of 8863 years. Patients were excluded from the study if they had genetic syndromes, colorectal surgery, or inflammatory bowel disease. An FIT was offered yearly, in the interval between colonoscopies; if results were positive, the colonoscopy was performed earlier than scheduled. **RESULTS:** Among the 1071 asymptomatic subjects (61%) who received at least 1 FIT, the test detected 12 of 14 cancers (86% sensitivity) and 60 of 96 (63%) advanced adenomas. In patients with positive results from the FIT, the diagnosis of cancer was made 25 months (median) earlier and diagnosis of advanced adenoma 24 months earlier. Patients who had repeated negative results from FIT had an almost 2-fold decrease in risk for cancer and advanced adenoma compared with patients who were not tested (5.5% vs 10.1%, respectively, $P = .0004$). The most advanced stages of neoplasia, observed across the continuum from nonadvanced adenoma to late-stage cancer, were associated with age (increased with age), sex (increased in males), and FIT result. The probability of most advanced neoplastic stage was lowest among those with a negative result from the FIT (odds ratio, 0.68; $P < .001$). **CONCLUSIONS: Interval examinations using the FIT detected neoplasias sooner than scheduled surveillances. Subjects with negative results from the FIT had the lowest risk for the most advanced stage of neoplasia. Interval FIT analyses can be used to detect missed or rapidly developing lesions in surveillance programs.**

Keywords: Colon Cancer; Colonoscopy; Colon Cancer Screening; Colon Cancer Testing.

Patients at increased risk for developing colorectal cancer (CRC) because of a family history or past history of colorectal neoplasia are recommended in professionally developed guidelines to have colonoscopic surveillance at regular intervals. Concerning family history, the risk for CRC is increased 3- to 6-fold in asymptomatic people who have 1 first-degree relative with CRC diagnosed before the age of 55 years[1–5] or 2 first-degree *or* 1 first- and 1 second-degree relative(s) on the same side of the family with CRC diagnosed at any age.[1,3,6] The National Health and Medical Research Council of Australia (NHMRC)[7] recommends that at-risk relatives (excluding familial syndromes) be referred for colonoscopy at 5-year intervals starting at age 50 years or 10 years younger than the age of the earliest diagnosis of CRC in the family, whichever comes first.[8] In those with a personal history of colorectal adenomas or cancer, where risk has been shown to be increased up to 8-fold,[9,10] the NHMRC recommends postpolypectomy surveillance intervals of the following: (1) within a year following incomplete or inadequate examination, (2) 3 years for subjects with cancer or advanced adenoma (ie, size ≥10 mm, high-grade dysplasia, villous change, or 3 or more adenomas), and (3) 5 years in the remainder. Many other guidelines make similar recommendations.

One concern in practice is the reliability of surveillance procedures and the consequences of delay in detection of missed lesions until the next scheduled colonoscopy. An additional concern is the possibility of rapidly progressive lesions that might develop in the years between scheduled colonoscopies. Recent guidelines have raised concern about colonoscopy quality and missed lesions.[11] Overall miss rates for neoplastic polyps in the literature range from 8%[12] to 24%,[13] the miss rates being higher for polyps smaller than 10 mm and polyps located at the splenic or hepatic flexure or at the cecum.[12] A recent Canadian study has shown that an apparently complete colonoscopy is associated with a reduction in deaths from

Abbreviations used in this paper: CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood tests; GFOBT, guaiac-based fecal occult blood tests; NHMRC, National Health and Medical Research Council of Australia.

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left-sided cancers but not from right-sided cancers.[14] They speculate that colonoscopy in the context of usual practice does not detect proximal lesions as well as might be anticipated. Such observations indicate the need to consider how best to manage the risk of missed lesions.

It is also relevant that, in recent years, evidence-based reviews have recommended extension of intervals between surveillance colonoscopies, although these have always been made with the caveat that any given colonoscopy should be of high quality with excellent views and adequate time being taken to identify lesions. For example, it has recently been recommended that patients with only 1 or 2 small (<10 mm) tubular adenomas with low-grade dysplasia have their next surveillance colonoscopy after an interval of 10 years on the grounds that risk is only marginally increased relative to the average-risk population.[11] For individuals participating in a colonoscopic surveillance program under these extended intervals, there is, therefore, a greater risk of delay in detection of rapidly progressing or missed lesions.

Additional surveillance strategies may be required to manage this risk. Undertaking annual fecal occult blood tests (FOBT) in the interval between surveillance colonoscopies could be a strategy that helps manage this risk by aiding detection of missed or rapidly developing neoplasms. Guaiac-based FOBT (GFOBT) are proven to be effective in 2-step screening of the general population for CRC,[15–18] even though the sensitivity of the original GFOBT (hemoccult II) is low.[17,19] A new type of stool blood test using an antibody specific for human hemoglobin, the fecal immunochemical test for hemoglobin (FIT), is being increasingly used because it is more sensitive for cancer and adenomas.[20–23]

The aim of this study was to undertake an initial evaluation of the use of FIT in the intervals between surveillance colonoscopies (ie, interval FIT). Specifically, we determined the following: (1) the sensitivity of interval FIT in asymptomatic subjects in this high-risk context, (2) the reduction in time to detection for lesions detected by an early colonoscopy triggered by a positive FIT, and (3) whether FIT result in the interval preceding diagnosis changed risk for the most advanced neoplastic lesion seen. This was achieved within a service-based surveillance program, by comparing outcomes in those who performed at least 1 interval FIT with those who did not. Adjustment was made for factors that might also affect risk for neoplasia, namely, age, sex, and interval between procedures.

Patients and Methods

Patients

Patients with a confirmed family or personal history of colorectal neoplasia were recruited into a colonoscopy-based surveillance program (a component of "SCOOP," the Southern Cooperative Program for Prevention of Colorectal Cancer) at Flinders Medical Centre, Flinders Private Hospital, and Repatriation General Hospital Daw Park. The initial reasons for being placed under surveillance were as follows: cancer and family history, n = 10; cancer, n = 398; adenoma and family history, n = 150; adenoma, n = 834; family history only, n = 344.

The study inclusion criteria required that patients had had at least an initial and 1 subsequent surveillance colonoscopy with adequate examination and retrieval of tissue, performed with a training-accredited colonoscopist present. Patients with hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, or inflammatory bowel disease were excluded from the study as were those in whom complete colonoscopic removal of lesions was not achieved.

NHMRC Australia ethical guidelines were followed for this study. Ethical approval was granted by the Research and Ethics Committee of the Repatriation General Hospital, Daw Park, and the Flinders Clinical Research Ethics Committee of Flinders University and the Southern Adelaide Health Service.

Colonoscopy Scheduling and Definition of Interval

The interval between colonoscopies was determined by the responsible physician but usually according to NHMRC recommendations.[7] These recommendations (excepting patients with hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, or inflammatory bowel disease) can be simply summarized as follows:

- 5-year colonoscopy: for individuals with a family history of CRC or personal history of small adenomas;
- 3-year colonoscopy: for individuals with a personal history of CRC or advanced adenomas; and
- colonoscopy within 12 months: if diagnostic procedure was incomplete or inadequate.

An "Interval" was defined as the period of time between 2 sequential colonoscopies. Certain individuals may have had more than 1 "interval" depending on the length of time they were in the program. Characteristics of an interval varied between and within cases according to whether the surveillance colonoscopy was "as-scheduled" or "brought forward."

Interval FIT

A brush-sampling FIT (InSure; Enterix Inc, Edison, NJ) was offered annually by mail to the participants in the intervening years between scheduled colonoscopies, offers commencing in 1999. The method of offer and process for reminders at 6 weeks followed that previously published.[24] If the FIT was not returned, the surveillance colonoscopy was offered as scheduled. The number of FIT performed within an interval varied according to the patient, uptake of the annual offer, and

duration of the interval. Consequently, some patients will have returned a negative FIT prior to a positive result.

Bringing Forward the Scheduled Colonoscopy

The scheduled surveillance colonoscopy was brought forward for either of 2 reasons: if an interval FIT returned a positive result or if a patient reported symptoms such as anemia, bleeding, change in bowel habit or abdominal pain considered sufficient by the responsible physician (primary care or colonoscopist) to warrant earlier colonoscopy. Information about symptoms was not routinely collected during an interval.

Cohorts and Analyses

The population, therefore, was composed of 2 principally self-determined cohorts: those who at any time undertook an FIT ("FIT-ever") and those who never undertook FIT ("FIT-never"). Both cohorts were further divided into those who always had routinely scheduled colonoscopy and those in whom colonoscopy was brought forward because of symptoms or to a positive FIT result. Pathologic status at the end of an interval was defined as the most advanced neoplastic diagnosis (confirmed by histopathology report).

To estimate test sensitivity in subjects in whom the interval was not influenced by symptoms, the FIT result was matched to the clinicopathologic diagnosis made at the end of the respective interval. Thus, sensitivity of FIT for neoplasia found at colonoscopy was able to be estimated on a program basis (any test positive among all the FIT performed within an interval) or on a single FIT test basis. For the program basis, where FIT was positive and colonoscopy brought forward, the FIT was considered to have "detected" the lesion regardless of prior negative results.

Statistical Analysis

For the analyses described, the data set was organized so that the first worst *surveillance* colonoscopy result over all intervals for a patient was identified as the dependent variable: "worst status." Additionally, the initial colonoscopy result (as opposed to subsequent surveillance) was not included because we had limited information prior to this event. Intervals in which colonoscopy was brought forward because of symptoms were excluded from the analysis. Independent variables included in analyses were age at test result, sex, a socioeconomic status index (Socio-economic score: Socioeconomic Index For Areas [SIEFA] Index of Relative Socio-economic Advantage and Disadvantage).[25] Indexes are scaled to 1000 with a standard deviation of 100, time interval since the preceding colonoscopy, family history of CRC, whether a patient underwent an FIT in the interval between colonoscopies, and whether the test was positive or negative (coded as "NoFIT" [FIT-never], "positive FIT," or "negative FIT").

Risk for neoplasia according to the characteristics of an interval was explored using multivariable proportional odds logistic regression using both forward and backward variable selection procedures. This was employed to explicitly account for the different stages of neoplasia. That is that the severity of neoplasia is measured on an ordinal scale with non-neoplasia the lowest stage and advanced adenoma/cancer the highest stage. Advanced adenomas and cancers were combined into 1 category to account for the low numbers of cancers. The Score test was used to test the proportional odds assumption to ensure that parameters varied in the same manner irrespective of different response levels. Because the Score test may be sensitive to small sample sizes, plots of binary model score residuals were visually inspected to determine whether the assumption held. If this assumption was rejected, multinomial models were implemented.

Cox proportional hazards was used to model the "reduction in time to diagnosis." Worst status was used as the event variable, with time to event taken as time in days since entry into the surveillance program. Median survival times (time to colonoscopy) were used to compute the reduction in time to diagnosis. Statistical tests were 2-sided, with $P \leq .05$ considered significant. Statistical analyses were performed using R software.[26] Differences in rates of neoplasia observed in different categories of "interval" were compared by χ^2 test unless there were fewer than 5 events, in which case the Fisher exact test was used.

Results

Patient Characteristics

There were 1736 patients who participated in the colonoscopic surveillance program who were eligible for the study. The data set comprised 8863 person-years of surveillance. There were 1071 in the FIT-ever cohort (61%), ie, patients who had performed at least 1 interval FIT. The demographic characteristics of *patients* at entry into the program according to sex and age, and their worst surveillance neoplastic outcomes, are shown in Table 1. Age distribution did not differ significantly between cohorts ($P = .256$, Pearson χ^2 test). Thirty-two people developed cancer, and 200 developed advanced adenoma, as the most advanced lesion at some time during surveillance. There were proportionally less women in the FIT-never (390 males/276 females) compared with FIT-ever cohort (534 males/536 females; $P < .05$, χ^2 test).

Surveillance Interval Outcomes

A total of 2520 surveillance intervals were assessable in the 1736 patients. The types of colorectal neoplasia observed at the end of each surveillance *interval*, according to whether the colonoscopy was brought forward and the reason for bringing it forward, are shown in Table 2. It should be noted that some patients had cancer or adenoma diagnosed at the conclusion of

Table 1. Patient Population Characteristics and Subgroups According to Whether or not a Person Performed a FIT, the FIT Result, and Whether or not Colonoscopy Was Brought Forward Because of Symptoms

	FIT-ever n = 1071 (61%)			FIT-never n = 665 (39%)	
Cohort (N = 1736) subcohort	At least 1 positive FIT[b] n = 397	Always negative FIT[c] n = 579	Symptomatic[a] n = 94	Routine colonoscopy n = 565	Symptomatic[a] n = 101
M:F	196:201	288:291	50:44	331:234	59:42
Median age, *y* (IQR)	65 (56–70)	61 (53–68)	67 (62–75)	66 (52–75)	70 (54–77)
Persons with cancer[d]	14	3	1	11	3
Persons with advanced adenomas[d]	67	46	17	57	13

IQR, interquartile range.
[a]Colonoscopy brought forward at some point because of symptoms deemed worthy of investigation.
[b]A positive FIT resulting in bringing forward a scheduled colonoscopy.
[c]No colonoscopy ever brought forward.
[d]Most advanced diagnosis ever made during surveillance.

more than 1 interval. It can be seen from Table 2 that cancer or advanced neoplasia was least likely in those intervals in which FIT tests were done but were consistently negative (5.5% compared with 15.2%). Conversely, the highest chance of cancer or advanced adenoma was seen in those in whom colonoscopy was brought forward because of either a positive FIT or symptoms. Nonadvanced adenomas were distributed approximately equally between the groups (Table 2), consistent with failure of FIT or symptoms to predict the presence of these early neoplastic lesions. In those intervals in which a FIT was done, the median number done was 2.0, and the range was 1–6.

Duration of Intervals

Figure 1 shows the interval duration between colonoscopies according to whether a FIT was done in the interval, the FIT result, or whether symptoms initiated the colonoscopy. For patients who returned a positive FIT, it can be seen that 62.2% had an interval of 30 months or less. Intervals in patients with negative FITs were mostly 3 years and 5 years as expected from the guidelines. Whereas there were peaks in FIT-not-done intervals at around 3 and 5 years, it can be seen that a proportion of intervals was less than 18 months. Many of these short intervals followed a finding of neoplasia at the colonoscopy marking the start of the interval: 85 (25.6%) with cancer and 87 (26.2%) with advanced adenoma. Many of these short intervals occurred in the early stages of the program prior to the promulgation of the NHMRC guidelines.[7]

For intervals in which the colonoscopy was brought forward by symptoms, the distribution of interval duration was fairly even, but numbers were small. The nature of the symptoms that brought forward colonoscopy were as fol-

Table 2. Most Advanced Neoplasia Found at Colonoscopy at the End of Each Surveillance Interval According to the Nature of the Interval and Whether or not Colonoscopy Was Brought Forward

Nature of interval	Number of intervals	Nonadvanced adenomas, n (proportion)	Advanced adenomas, n (proportion)	Cancer, Dukes stage, n (%)					Advanced adenoma or cancer, n (%)	Comparison of intervals, *P* = significance[a]
				A	B	C	D	All cancer		
1. FIT not done, colonoscopy as scheduled	1157	186 (16.1%)	102 (8.8%)	8	3	3	1	15 (1.3)	117 (10.1)	.95 (vs 2) .0004 (vs 2.1) .004 (vs 2.2) .048 (vs 3)
2. FIT done, colonoscopy according to result	1170	189 (16.2%)	96 (8.2%)	6	3	4	1	14 (1.2)	110 (9.4)	.002 (vs 2.1) .0007 (vs 2.2) .019 (vs 3)
2.1 FIT negative, colonoscopy as scheduled	697	101 (14.5%)	36 (5.2%)	1	1	0	0	2 (0.3)	38 (5.5)	.0001 (vs 2.2) .0001 (vs 3)
2.2 FIT positive, colonoscopy brought forward	473	88 (18.6%)	60 (12.7%)	5	2	4	1	12 (2.5)	72 (15.2)	.55 (vs 3)
3. Symptoms, colonoscopy brought forward	195	28 (14.4%)	23 (11.8%)	1	5	0	0	6 (3.1)	29 (14.9)	

[a]χ^2, with Yate's correction; nonsignificant = $P > .05$.

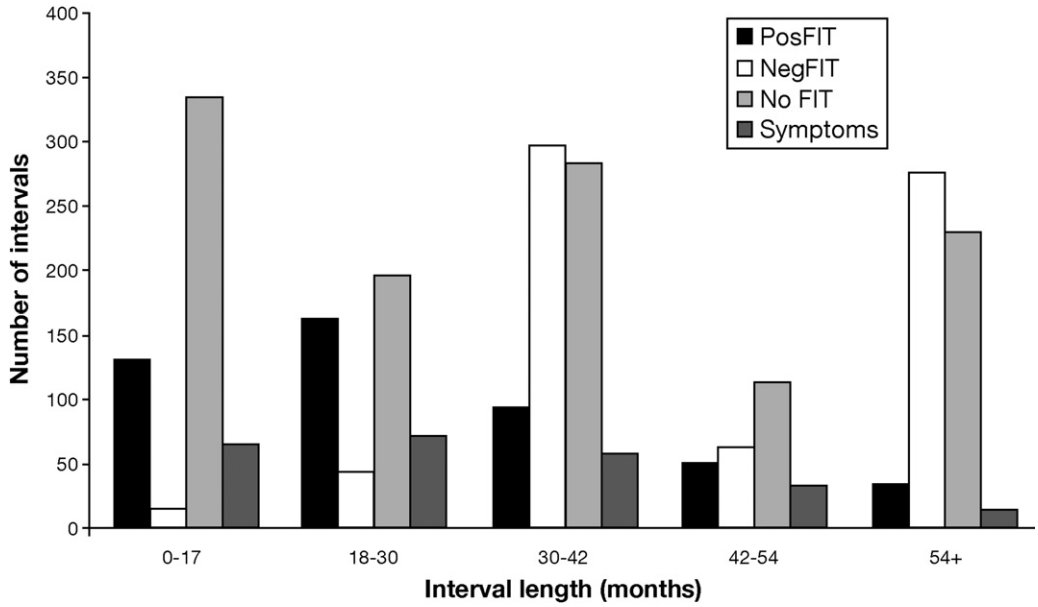

Figure 1. Distribution of duration of interval between colonoscopies according to the nature of the interval (ie, according to whether a FIT was done in the interval, the FIT result, and whether symptoms affected interval length).

lows: anemia, 17.9%, overt rectal bleeding, 50.3%; change in bowel habit, 17.4%; abdominal pain, 5.6%; and other, 8.7%.

FIT Sensitivity for Neoplasia

Within an interval, a number of negative FIT tests might have preceded the positive that brought forward the scheduled surveillance colonoscopy and "detected" the neoplasia. Consequently, sensitivity for neoplasia was estimated both on a program and a single test basis (see Patients and Methods section).

Neoplasms found in asymptomatic intervals in which at least 1 FIT was done are described in Table 3 according to FIT result together with calculation of sensitivity and likelihood ratio for a positive test for each category of neoplasia. Fourteen cancers were observed at either brought-forward or scheduled surveillance colonoscopy, and 12 of these were detected by a prior positive FIT (program sensitivity for cancer of 86%). Similarly, 96 advanced adenomas were observed, and 60 of these were found at brought-forward colonoscopy because of positive FIT (program sensitivity for advanced adenoma of 63%). The program sensitivity for significant neoplasia (cancer or advanced adenoma) was 65.5% and for any neoplasia was 53.5%. If results were analyzed on a once-only test basis, sensitivities and likelihood ratios were lower (Table 3) as would be expected.

We also calculated sensitivity including cases in which colonoscopy was brought forward because of symptoms because a few of these had returned a negative FIT prior to reporting symptoms. Sensitivity for cancer was unchanged, but program sensitivity for advanced adenoma fell to 54.8% and for small adenomas to 44.2%; respective once-only sensitivities also fell to 36.3% and 24.0%, respectively.

Of the 6 stage A cancers in the FIT-done group, 5 were FIT positive. Of the 12 cancers detected by FIT, 4 (3 of which were stage A cancers) had a preceding negative FIT test. Of the 2 cancer cases not detected by FIT, each patient completed just 1 FIT test in the interval preceding the colonoscopy.

Table 3. Program and Once-Only Sensitivity of FIT for Various Classes of Neoplasms Found in Intervals in Which at Least 1 FIT Was Done, Together With Likelihood Ratio for a Positive Test for Each Category of Neoplasia

Neoplasia diagnosis[a]	Positive FIT in interval leading to detection (program sensitivity, 95% CI)	Likelihood ratio (95% CI)	Positive FIT tests/FIT tests done (once-only sensitivity, 95% CI)	Likelihood ratio (95% CI)
Cancer, n = 14	12 (85.7%, 57.2−98.2)	2.63 (2.07−3.33)	12/18 (66.7%, 41.0−86.6)	2.38 (1.69−3.36)
Advanced adenoma, n = 96	60 (62.5%, 52.0−72.2)	1.92 (1.59−2.31)	60/145 (41.4%, 33.9−50.5)	1.50 (1.21−1.87)
Significant neoplasia, n = 110	72 (65.5%, 55.8−74.2)	2.00 (1.69−2.38)	72/163 (44.2%, 37.0−52.8)	1.60 (1.31−1.96)
Small adenoma, n = 189	88 (46.6%, 39.3−53.9)	1.43 (1.19−1.72)	88/351 (25.1%, 20.6−29.9)	0.9 (0.73−1.10)
Any neoplasia, n = 299	160 (53.5%, 47.7−59.3)	1.64 (1.42−1.90)	160/514 (31.1%, 27.3−35.5)	1.12 (0.95−1.32)

CI, confidence interval.
[a]Most advanced diagnosis in the interval.

Table 4. Reduction in Time to Diagnosis (Uncorrected for Age, Gender, and Family History of CRC) in Cases Detected by a Positive FIT and in Whom Colonoscopy Was Brought Forward From the Scheduled Time

Diagnosis	Median reduction in time to diagnosis in months, (interquartile range)
Cancer A, n = 5	17.5 (7–20)
Cancer B, n = 2	21.8
Cancer C, n = 4	37.9 (34.9–42.4)
Cancer D, n = 1	44.3
Advanced adenoma, n = 60	18.4 (9.2–28.5)

Time to Detection of Neoplasia

The reductions in time to diagnosis for cancer by stage and for advanced adenoma (uncorrected for age, sex, and family history) are shown in Table 4 for cases in which colonoscopy was brought forward because of a positive FIT. Using a Cox proportional hazards model to adjust for age, gender, and family history of CRC, median reduction in time to diagnosis for cancer was 25 months and for advanced adenomas was 24 months.

Effect of FIT Testing on Stage of Neoplasia

Table 5 shows odds ratio for most advanced stage of neoplasia as indicated by FIT result adjusted for variables in the preceding surveillance *interval*. Because several variables are likely to influence stage distribution in addition to result of FIT, a multivariate proportional odds logistic regression was undertaken as outlined in the Patients and Methods section. As can be seen from Table 5, the odds of reaching the most advanced stage (ie, advanced adenoma or cancer) increased with increasing age and male sex but not interval between colonoscopies or socioeconomic status. Family history as an entry indication reduced the odds marginally relative to those with a personal history. The odds for finding advanced adenoma or cancer were reduced by 32% (1 to 0.68 as shown in Table 5) if a FIT was done and tested negative. The odds were not reduced if a positive FIT occurred within an interval, as would be expected because a positive FIT biases toward diagnosis. A multinomial model, where each stage of severity of neoplasia was modeled separately, showed that those patients with either cancer or advanced adenomas (highest stage) had more positive than negative FIT results, whereas the converse was true for cases with nonadvanced adenomas or a nonneoplastic status; none was significant at the $\alpha = .05$ level; data not shown.

Discussion

A major concern in surveillance of patients at increased risk of CRC is that of rapidly developing or missed lesions. It has been established that cancers develop quite rapidly for some pathways of oncogenesis. It is also clear that colonoscopy in usual practice is not a perfect test, and lesions can be missed.[11,14] In clinical practice as evidenced in this study, the actual intervals between colonoscopies vary widely despite guidelines, and colonoscopy may be performed more frequently than necessary, presumably because of concern for missed lesions and lesions with a more rapidly evolving biology.[27]

The principal aim of this study has been to determine whether there is value in fecal occult blood testing using a FIT between scheduled surveillance colonoscopies when colonoscopy is provided as a scheduled service for people at increased risk for CRC. We addressed the aim in 2 ways. One was to determine how well neoplastic lesions arising in such patients were detected by a FIT. The other was to determine whether detection was likely to be worthwhile by ascertaining how much earlier such lesions were detected and whether risk for the most advanced lesion was altered.

In our study, 1736 cases were recruited over 17 years and observed for 8863 person-years of surveillance. One thousand seventy-one cases (61.7%) participated in FIT on at least 1 occasion, and an average of 1.8 FITs were done in each interval. The willingness by many individuals in a high-risk surveillance program to participate even though they already have the assurance of colonoscopy being scheduled at some point in the reasonably near future confirms our earlier findings in a more limited study.[28] It was interesting that FIT-never patients tended to be scheduled for colonoscopy earlier than the usual 3- or 5-year intervals, which might have led to them feeling less in need of the reassurance of an interval FIT.

Table 5. Odds Ratio for Most Advanced Stage of Neoplasia as Indicated by the Variables Status of FIT, Adjusted by Age Group, Sex, Duration of Interval, Socioeconomic Status, and Family History in a Proportional Odds Logistic Regression Analysis

Factor	Odds ratio (95% CI)
Age group (*y*)	
<50	1.00
50–60	1.77 (0.91–3.43)
60–75	2.08 (1.12–3.84)
>75	2.33 (1.21–4.51)
Sex	
Female	1.00
Male	1.47 (1.11–1.95)
FIT outcome	
Not done	1.00
Negative	0.68 (0.46–1.01)
Positive	1.10 (0.71–1.70)
Family history of CRC	
Personal history of CRC	1.00
Family history	0.69 (0.49–0.97)
Socioeconomic score	0.81 (0.65–1.01)
Interval between colonoscopies	1.15 (0.92–1.44)

NOTE. An odds ratio >1 indicates increased odds of significant neoplasia (ie, cancer or advanced adenoma).
OR, odds ratio.

The sensitivity of FIT for neoplasia can be assessed in 2 ways in our program. The first is the programmatic approach, ie, for any surveillance interval when a FIT was done and neoplasia was detected at subsequent colonoscopy (whether brought forward or as scheduled), did the FIT detect the neoplasia? The programmatic sensitivity in asymptomatic subjects of the FIT used in the study (InSure) was 86% for cancer and 62% for advanced adenomas. For cancer, this is an excellent rate, falling at the upper end of the range of cancer detection by a FOBT.[29] It is also one of the highest reported detection rates by a FOBT for advanced adenomas, confirming the value of FIT in assisting detection of advanced adenomas.

Detection rates for FIT can also be determined by calculating sensitivity of a single test ("once-only" sensitivity) for neoplasia. In asymptomatic patients subsequently shown to have cancer at the end of an interval, 67% of FIT done in the interval were positive. This equates to a 67% once-only sensitivity for cancer. The once-only FIT sensitivity for advanced adenomas was 41%. The once-only calculation underestimates the actual detection rate (sensitivity) because such lesions might not necessarily have been present on every occasion the FIT test was undertaken.

It is important that FOBT screening was never meant to be the once-only performance of a test—the evidence base for effectiveness requires repeated testing.[15–18] Our data clearly demonstrate that repeated testing results in a compounding of sensitivity. We observed that programmatic sensitivity for cancer compounded to 86% and, on average, people did 1.8 FIT per interval. This corresponds almost exactly to the results of modeling detection (assuming unbiased detection each time testing is done) where it can be calculated that a once-only sensitivity of 67% compounds to 89% with just 2 rounds of testing. Similarly for adenoma detection, modeling a 41% once-only sensitivity compounds over 2 rounds of testing to 65%, which compares closely with our programmatic observation of 62%.

Two previous smaller studies have suggested that interval FOBT testing is capable of detecting cancer in the setting of a high-risk surveillance program. Skaife et al detected 9 cancers in their study of 611 patients where FIT were performed on stool samples obtained by digital rectal examination.[30] We reported on our early experience where once-only interval FIT detected 6 cancers and 8 advanced adenomas.[28] The present much larger study clearly shows that interval FIT does aid detection of missed or rapidly developing neoplasms.

Given that FIT were capable of detecting interval lesions, we calculated how much earlier the diagnosis was made compared with what would have been the case if the surveillance colonoscopy were performed as scheduled. The 12 FIT-detected cancers were detected on average 25 months earlier (after correction), whereas the 60 with advanced adenomas were detected on average of 24 months earlier. It is impossible to determine whether the earlier detection of advanced adenomas prevented progression to cancer by the time of the scheduled colonoscopy, but reducing the time to diagnosis would be anticipated to be reflected in distribution of cases detected across the stages of oncogenesis. This would manifest as not just a shift to earlier stage cancers but also a shift to adenoma rather than cancer because adenomas are a precursor to cancer. Consequently, we expressed stage distribution as a continuum from non-neoplasia through nonadvanced and advanced adenoma to cancer (in its various stages).

Examination of the distribution of the cohorts across the stages did not initially reveal an obvious down-staging effect, but several issues need consideration. A range of other measurable variables can impact on stage distribution including age, sex, family history of CRC, FIT performance and results, socioeconomic status, and length of interval. Therefore, these were included in the analysis, having excluded intervals in which symptoms resulted in colonoscopy being done sooner. This demonstrated that FIT results were significantly associated with risk for the most advanced stage of neoplasia (Table 5) because the probability of advanced neoplastic stage was reduced in those who returned only a negative FIT. Those who had consistently negative FIT were less likely to have advanced neoplasia compared to those who were non-FIT participants (5.5 vs 10.1%, respectively; $P=.0004$; see Table 2). Thus a consistently negative FIT result could be used to lengthen intervals between colonoscopies when colonoscopic resources are constrained.

In view of the design of the program, we were able to make an assessment of the value of bringing colonoscopy forward as a consequence of self-reported symptoms that the primary-care practitioner and colonoscopist felt warranted earlier investigation. Whereas the number of such cases was relatively small and the spread of symptoms wide, 3.1% had cancer and 11.8% had advanced adenomas (Table 2). Given this risk, bringing forward the scheduled colonoscopy because of self-reported symptoms seems justified. We cannot exclude the possibility that a person did a FIT because of symptoms that remained unreported. This does not change the utility of bringing forward colonoscopy as a result of a positive FIT.

It is unclear whether the interval lesions detected in our study represent lesions missed at the prior colonoscopy or lesions that have rapidly progressed in the interval. The interval cancers and adenomas were not obviously different in any way including site distribution in the colon (data not shown). Genotyping neoplastic lesions might help to identify rapidly progressing lesions (eg, microsatellite instability), but, even in a large study such as this, the actual number of affected cases is small. This is an area in which further research might be informative.

The strengths of this study were the large number of cases undergoing surveillance, the frequency of neoplastic events (although cancer cases remained low), over 8000 person-years of observation, and the reality of the service-delivery setting. The weaknesses were that cases were not randomized, that colonoscopic intervals were not tightly controlled according to best practice especially in the early stages of the study, and that patterns of FIT usage and nonusage were understandably random. A prospective randomized study might be able to resolve any uncertainties, but this would take a decade to reach useful conclusions.

There are limitations to this study. It reports on self-selected cohorts in the context of usual practice. Thus, bias because of variations in practice are unavoidable, and nonmedical influences such as socioeconomic status might affect decision making by the patient. A combination of physician and individual behavior did influence interval lengths as shown (Figure 1), and interval length was included in the multivariate analysis where it failed to be a significant factor. Variations in physician response to reported symptoms were minimized by removing cases from calculations of sensitivity and from the multivariate analysis where it was known that the colonoscopy was brought forward for that reason. We cannot, however, exclude unreported symptoms as being a reason for some doing a FIT; this might result in estimates of FIT sensitivity being a little higher than would be the case for asymptomatic subjects as described. On the other hand, if this is a strategy for getting symptomatic cases to colonoscopy, then it remains useful in practice. Low socioeconomic status tends to be associated with noncompliance with preventive strategies, including participation with FIT-based screening[24] and reporting of symptoms of concern; consequently, there could be overrepresentation of such cases in the FIT-never cohort. However, socioeconomic status was not a significant risk factor for the most advanced neoplastic status (Table 5). These variables could only be minimized by a prospective randomized study, which, if feasible, would clarify the situation further. In the meantime, the findings identify a strategy for detection of rapidly developing or missed lesions.

In conclusion, this initial evaluation of the use of FIT in the intervals between surveillance colonoscopies in a high-risk population has demonstrated that such "interval testing" aids detection of cancer and advanced adenomas that were either missed or that developed rapidly in the interval. Cancer and advanced adenomas were detected much sooner than would have happened at scheduled surveillance. In those who consistently returned a negative FIT, the chance of finding cancer or advanced adenoma was significantly reduced. Interval FIT testing in a high-risk colonoscopy surveillance program is useful as a strategy for detecting missed or rapidly developing lesions.

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Conflicts of interest

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