Population Colorectal Cancer Screening with Fecal Occult Blood Test

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Abstract

Screening for early detection of colorectal cancer using fecal occult blood testing has been shown to be effective in reducing mortality from this disease. The largest Health Maintenance Organization in Israel initiated the use of Hemoccult Sensa in 1992 to evaluate the field performance of this test. All primary care physicians were invited to order home-based tests for their asymptomatic patients 50–74 years of age. This report summarizes the results of 45,166 tests performed, 22,193 in the prevalence round. Seventy-eight cancers, 60 patients with adenomas, and 163 patients with polyps were detected, yielding a cancer detection rate of 2.61/1,000 screened in the prevalence round. Of these, 21.6% were in the right colon. Of screen-detected cancers, 44.5% and 58.9% were detected in Dukes' A and *in situ* stages in the prevalence and incidence rounds, correspondingly. The overall estimated sensitivity of the test (median follow-up, 35 months) was 85.3% for the prevalence round with a specificity of 95.5%. The sensitivity for left-side tumors (87.9%) was higher than for right-side or rectal tumors (78.6%). The positive predictive value for cancer increased with increasing number of positive fields. Four or more positive fields had a positive predictive value for cancer of 16–26% and a positive predictive value of 46–71% for all tumors combined. Population screening with a sensitive fecal occult blood test performs well outside a trial setting, detecting a high proportion of expected tumors with favorable stage distribution. Given its proven power to significantly reduce mortality, use of this test is strongly advised to both medical organizations and the healthy population at average risk.

Introduction

Screening for colorectal cancer using FOBTs[2] has now been shown in three randomized trials to be effective in reducing mortality from this type of cancer (1–3). Although several policy-making agencies have already published guidelines for screening, experience in using this type of test with the general population, outside the framework of a trial, is limited (5–7). Other cancer screening activities, such as mammography screening for breast cancer, have helped formulate a list of process and outcome parameters that serve as markers of the potential success of a screening program (8). Among them are the detection rate, test positivity rate, early stage rate, and interval cancers rate.

When FOBT tests were first shown to have a potentially positive effect on colon cancer detection, the largest Health Maintenance Organization-type organization in Israel (CHS) decided to initiate an early detection pilot activity. This was done to study the field performance and yield of this technology in the general asymptomatic population.

Materials and Methods

All primary care physicians in CHS (>2,000) were offered the opportunity to order free-of-charge FOBT kits for their asymptomatic patients 50–74 years of age. All requested test kits were mailed by the testing center directly to the homes of the insured patients. The test kit included one Hemoccult Sensa (SKD, Inc.) 3-day card (six windows); a detailed instruction sheet (including dietary and drug restriction list); and a questionnaire including demographic information, a risk factor profile, and a list of possibly relevant symptoms. In addition, participants were provided with a temperature-protection aluminum return envelope, which is of special importance when taking into account Israel's hot weather. All tests were returned by mail to one central laboratory and processed, without rehydration, by a single laboratory technician using the manufacturer's reagent. It is estimated that the kits were processed between days 3 and 4 from the date of postmark, or ~7 days after the performance of the home examination. Results were coded as negative, traces, or positive in each of the six relevant test windows and were then mailed to the participant's primary care physician along with two documents: (*a*) Guidelines for the evaluation of a positive test result as set by the gastroenterology consultants of CHS (these included a recommendation for full colonoscopy or sigmoidoscopy plus double contrast barium enema. Repeated FOBT was discouraged); and (*b*) a form to report all performed follow-up tests and their results to the testing center. These were classified into: normal; non-tumor finding possibly explaining the positive test; nonmalignant tumor (with subdivisions to polyps and adenomas of all histological types and sizes); and malignant tumor. Histological diagnoses were recorded as they appeared in the respective pathology laboratory where the patient's tissue was evaluated.

After performing the test for the first time, patients were automatically reissued Hemoccult Sensa cards annually by mail. The list of all participants in the screening activity was matched (using ID number, last name, and first name) with the colorectal cancer file of the Israel Cancer Registry. The Cancer Registry file is updated to the end of 1997.

Results were analyzed separately by first (prevalence)

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[2] The abbreviations used are: FOBT, fecal occult blood test; PPV, positive predictive value; CHS, Clalit Health Services.

Table 1 Characteristics of the screened population, prevalence round

	All first screened	All with screen-detected cancer	Significance (cancer *vs.* no cancer)
Mean age	61.33 ± 8.55	65.76 ± 6.79	$P < 0.001$
Sex			
Male	10,123 (45.6%)	36 (62.1%)	
Female	11,855 (53.4%)	22 (37.9%)	$P = 0.01$
Origin[a]			
Ashkenazi Jews	16,227 (73.1%)	46 (80.7%)	
Sephardi Jews	4,466 (20.1%)	9 (15.8%)	
Israeli	1,551 (3.8%)	3 (3.5%)	Not significant
Family history			
First degree	2,804 (12.6%)	6 (10.3%)	
Second degree only	1,153 (5.2%)	7 (12.1%)	$P = 0.06$
None	18,236 (82.2%)	32 (77.6%)	

[a] Ashkenazi, subject or parents born in Europe/America/Oceania/South Africa; Sephardi, subject or parents born in Asia/Africa; Israeli, subject born in Israel, parents born in Israel, or from mixed origins.

Table 2 Detection utilities (and 95% confidence interval) of FOBT in a screening set-up

Round	Specificity	Sensitivity[a]	PPV		
			Cancer	Tumor[b]	Any finding[c]
1 (n = 22,193)	95.5 (90.6–100.0)	85.3 (76.9–93.7)	5.5 (0.0–11.0)	26.6 (20.2–32.9)	52.9 (47.8–58.0)
2 (n = 10,780)	96.6 (86.7–100)	69.2 (62.3–94.3)	2.4 (0.0–10.7)	19.0 (7.5–30.4)	46.0 (36.6–55.3)
3 (n = 6,260)	97.0 (85.3–100)	100	4.1 (0.0–17.9)	18.7 (2.8–34.6)	48.0 (35.2–60.7)

[a] Sensitivity based on a median follow-up period of 35 months for round 1, 25 months for round 2, and 20 months for round 3.
[b] Cancer, adenoma, polyp.
[c] Cancer, adenoma, polyp, diverticulosis, hemorrhoids.

Table 3 Demographic characteristics of colorectal cancer detection rate by screening round

	Round 1	Round 2
Overall	2.61/1000	0.84/1000
Age		
50–59	1.72	0
60–74	3.19	1.19
75+	8.35	5.29
Origin		
Ashkenazi	2.83	1.07
Sephardi	2.02	0
Israeli	1.93	0
Sex		
Male	3.56	1.03
Female	1.86	0.68

Table 4 Location in colon of prevalence round colorectal cancers

Location	Screen-detected	Screen-missed	Sensitivity
Right and transverse colon	11 (21.6%)	3 (30%)	78.6%
Left and sigmoid colon	29 (56.9%)	4 (40%)	87.9%
Rectum	11 (21.6%)	3 (30%)	78.6%

round and second or more (incidence) rounds. Test performance results (finding-specific) are presented in terms of sensitivity, specificity, and PPV. Operation parameters include the positivity rate, detection rate, and small tumor rate.

Results

During a period of ~5 years, 45,166 tests were performed in the National Cancer Control Center of CHS. Of these, 22,193 tests were first tests, and 23,088 were repeated screens. Fifty-nine cancers were detected in the first screening round in this population, one of them in the stomach. Another 10 cancers were missed by screening, whereas 19 more cancers were detected in subsequent screening rounds. In addition, 60 adenomas and 163 polyps were diagnosed in the study population. Tumors in the first round were more often diagnosed in older males of Ashkenazi origin (Table 1). Family history was reported by ~20% of the participants.

Test Performance. The performance characteristics of the tests, by test round, are shown in Table 2. Mean follow-up time after the first round of FOBT tests was 34.1 months (±18.8) with a median of 35 months and a range of 1–71 months. Only 37.2% of the cases had a follow-up period shorter than 24 months. Because of the lag in the update of the Israel Cancer Registry (currently updated until the end of 1997), the sensitivity figures may be slightly overestimated. In each of the years 1994–1997, the missed cancer rate (based on Israel Cancer Registry data) was 2.5–4% of the screen-detected rate. If these false-negative rates are kept for 1998–1999, then an overall overestimation of the sensitivity of this magnitude is possible.

Positivity Rate. In the first round of 22,193 tests, 1,035 (4.7%) were found to be positive in one or more of the windows.

Detection Rate. The detection rate for colorectal cancer in the first round was 2.61/1,000. Detection differed by age, origin, and sex (Table 1). Rates were higher among the Ashkenazi population. Rates in both rounds were much higher in males than in females (Table 3).

Location. Most cases were detected, as expected, in the left colon (Table 4). Yet more ascending colon tumors and fewer left colon and rectal tumors were detected among females than among males (Table 5). Tumors were more often missed by the FOBT if they were in the rectum or in the right and transverse colon.

In the prevalence round, >60% of the screen-detected tumors were *in situ* or Dukes' stages A and B (Table 6). Stage distribution was far improved in the repeated (incidence)

Table 5 Sex differences in location in colon of screen-detected colorectal cancers in the prevalence round

Location	Males	Females
Right colon	4 (12.9%)	5 (25.0%)
Transverse colon	2 (6.5%)	0 (0%)
Left and sigmoid colon	18 (58.1%)	11 (55.0%)
Rectum	7 (22.6%)	4 (20.0%)

Table 6 Stage distribution of screen-detected colorectal cancers in prevalence and incidence rounds

Stage at diagnosis	Prevalence round	Incidence rounds
In situ	7 (13.0%)	2 (11.8%)
A	17 (31.5%)	8 (47.1%)
B	10 (18.5%)	4 (23.5%)
C	15 (27.8%)	2 (11.8%)
D	5 (9.3%)	1 (5.9%)
Unknown	4	0

rounds of the screening. Similar stage distribution was found in males and females. Diagnosis of the missed cases was done with a mean of 5.2 (range, 0–12) months after the negative FOBT.

Number of Positive Fields. Tumors were detected among people with any number of positive FOBT fields (Table 7), yet the positive predictive value for cancer of four to six positive fields was much higher than that for traces or one to three positive fields. Three to six positive fields were a better cutting point for a high PPV for any tumor (cancer, adenoma, or polyp; Table 8).

Table 7 Number of positive FOBT fields in people screen-detected in the prevalence round with colorectal cancer

No. of positive fields	No. of cases
Traces	2 (3.4%)
1	11 (19.0%)
2	7 (12.1%)
3	6 (10.3%)
4	11 (19.0%)
5	8 (13.8%)
6	13 (22.4%)

Table 8 PPV by number of positive FOBT fields in people with screen-detected tumors in the prevalence round

No. of positive fields	PPV for cancer $n = 58$	PPV for adenomas $n = 44$	PPV for polyps $n = 103$	PPV for all tumors
Traces	0.8	3.1	10.1	13.8
1	3.2	8.0	13.5	24.0
2	3.4	3.7	13.4	20.9
3	8.2	12.2	24.5	46.9
4	15.9	7.3	22.0	46.3
5	25.8	19.0	33.3	71.4
6	19.4	2.3	16.3	41.9

Discussion

Taking screening activity from a research setting to practice in the community is a complicated task (9). Crucial to its success are both a high uptake rate by the population and good detection performance (7, 8). The FOBT, shown in three randomized controlled trials to be effective in reducing mortality from colon cancer (1–4), is an optimal test for large, average-risk populations. It is cheap, easy to perform, noninvasive, and has good detection characteristics, yet needs to be performed annually and calls for a strict diet and personal handling of feces. This test, however, suffers from a low technological image. This leads many small medical practices to analyze FOBT tests without paying enough attention to crucial quality issues, such as the dietary recommendations, the timing of the test development, and the quality of the color reaction. Low-quality processes can render the entire detection effort useless. Our facility has handled close to 50,000 tests over a 5-year period. All cards were read by only two technicians. The tests were provided to participants with all necessary written explanations, were carried out on 3 consecutive days with two windows used on each day, and were followed up to ensure proper handling of the test results by the medical teams. The tests were provided in a temperature-protecting envelope and were read about 1 week after the application to the first window. This passage of time is now thought to increase the sensitivity of the test (10). Instead of using rehydration, we chose the more sensitive test, Hemoccult Sensa.

From the results of our series, it can be seen that achieving a high detection rate in a well-organized community set-up is feasible. The detection rate of 2.6/1000 in the prevalence round was, as expected, ~1.5 times higher than the incidence rate reported by the Israel Cancer Registry for this age group (11). Also as expected, the detection rate in the Sephardi group was lower than the rate in the Ashkenazi group.

The 2-fold higher detection rate in males as compared with females is not in line with the relatively similar incidence of colorectal cancer in both sexes in Israel and in other Western countries (11, 12). This gap in detection was reduced by one-half in the incidence round. One possible explanation is a higher proportion of neglected tumors in males, because of lower health awareness among males when compared with females (13). Another contributor to this difference may be the lower detection power of FOBT in women, reflecting the lower sensitivity of FOBT to right-side tumors, which are known to be more common in women (14). High detection rates were accompanied by high sensitivity and high specificity, mainly in the left colon, but also to a lesser extent in the right colon and the rectum. The slightly lower sensitivity in the rectum has been reported previously (6). More tumors were detected in the right colon in women than in men, which is in line with known statistics of colorectal tumor location (14). Our screening program has managed to maintain a low positivity rate. This is of utmost importance for population screening activities, because it is an indicator of the extent of the burden on the medical system that results from unnecessary tests and the burden of false-positive results on the patient.

The stage of tumors detected in the prevalence round shows a possible effect of neglected tumors, with some 37% of the tumors being detected at an advanced stage (Dukes' C and D). Yet the 63% detection of early, potentially curable tumors is a marker of a potential, future, positive effect on mortality reduction. In the incidence round, tumors were detected, as expected, in an even smaller size, with 82% of the tumors smaller than Dukes' stage C.

In summary, the described population-based screening program managed to achieve a high detection rate, a shift in tumor stage toward smaller tumors, a low positivity rate, and an acceptable false-positivity rate. FOBT seems to be an optimal

screening test in that it offers high sensitivity and specificity in the form of a noninvasive, home-performed, low-cost technology. Decision-makers should not be tempted to indulge in the more expensive, highly invasive procedures, not yet proven to be superior from the public health point of view. Nevertheless, engaging in FOBT screening should be done with the same attention to program construction and quality as in programs involving more complex technologies.

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