

Screening and Rescreening for Colorectal Cancer

A Controlled Trial of Fecal Occult Blood Testing in 27,700 Subjects

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All inhabitants of the city of Göteborg who in 1982 were between 60 and 64 years of age (27,700) were randomly divided into a test and a control group. The 13,759 subjects in the test group were invited to perform Hemoccult II (Smith Kline Diagnostic, Sunnyvale, CA) fecal occult blood testing over 3 days and to repeat the testing after 16 to 22 months. At the first screening 9,040 (66%) completed the test, and 7,770 (58%) completed the test at the second screening. In the first screening the test group was divided into two subgroups in which the tests were rehydrated and unhydrated before development. All tests were rehydrated in the second screening; 1.9% and 5.8% of the tests were positive in the unhydrated and rehydrated subgroups, respectively. The number of diagnosed neoplasms in the first screening was significantly larger ($P < 0.01$) in the rehydrated group compared to the unhydrated group, 50 and 24 neoplasms, respectively. Sixteen of 61 carcinomas in the test group were found in the interval between the two screenings, 19 of the carcinomas at the second screening, and ten among the nonresponders. Rehydration of the Hemoccult II test is a necessity. Significantly more carcinomas (61) were found in the test group compared to the control group (20). There was a trend toward favorable tumor staging in the test group compared to the control group.

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FIVE-YEAR SURVIVAL RATES in patients with colorectal cancer have been almost constant over the last couple of decades. This is the main reason for the interest in mass screening programs for early detection of colorectal neoplasms. Such mass screening is, for practical reasons, only possible by the detection of occult blood in feces. The test most often used for this purpose is the guaiac-impregnated filter paper test, which is not ideal as the test is not specific for hemoglobin. However, there are indications from uncontrolled studies that colorectal carcinomas diagnosed by means of guaiac screening are often localized.¹ A drawback of this method of screening is that other nonneoplastic bleeding lesions will also give a positive result.

The aim of occult blood testing is to reduce the mortality from colorectal cancer in the screened population.

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Whether this can be achieved can only be answered by the results of prospective controlled studies. Five such studies are underway, two in the United States and three in Europe. At the Memorial Sloan-Kettering Cancer Center the study is focused on the large bowel as the subjects in both the test group and the control group are sigmoidoscoped. Occult blood testing is offered to the subjects in the test group.² In another study performed in Minnesota 45,000 subjects 50 years or older were randomly divided into a control and two experimental groups, which are tested for occult bleeding yearly or every other year.³ The participants were selected from among health-conscious volunteers, which means that it is doubtful that the results will be representative of the population as a whole. The results will be presented in 1995. In England a study underway includes 26,975 patients from general practitioners lists. The compliance in this study is low, 38.5%.⁴ In Denmark a recently started study has a representative population from 45 to 74 years of age.⁵ Most of the ongoing studies thus focus on a special group of individuals. The need for more representative, randomized, controlled studies that reflect the general population is obvious. A controlled study in a sample that represents the general population was, therefore, started in Göteborg in 1982.⁶

The purpose of this study is to evaluate several factors

associated with this type of screening such as (1) the sensitivity and specificity of the test and of the methods of workup, (2) the compliance rate, (3) the distribution of the carcinomas according to the Dukes classification, (4) the effect on survival, and (5) the appropriate interval between repeated screenings. The answers to some of these questions require several more years of follow-up.

Materials and Methods

First Screening

The first screening study was performed between August 1982 and December 1983. All 27,700 inhabitants of the city of Göteborg born between 1918 and 1922 (60 to 64 years of age in 1982) were randomly allocated to a control or a test group. The control group consisted of 13,744 people, and the test group included 13,759 people. One hundred and ninety-seven people in the test group did not participate; 145 had died before the test slides were sent out, and 52 could not be located. The subjects in the control group were never contacted.

Three Hemoccult II tests (Smith Kline Diagnostic, Sunnyvale, CA), a letter of instruction, a questionnaire, and a postage-paid reply envelope were mailed to the subjects in the test group. The subjects were asked to perform Hemoccult II occult blood testing with two samples from each of three consecutive stools and to mail the slides back to the hospital immediately after the last test. Two reminder letters were sent out to subjects who did not answer. The last letter included another set of Hemoccult II slides.

In order to test the effect of rehydration, the test group was divided into two subgroups. Slides from persons born between January 1, 1918 and June 31, 1920 were not rehydrated before development, while slides from subjects born during the second half of the period were rehydrated before development. The people in the latter group were asked to maintain a low fruit and vegetable intake for two days before sample collection. The subjects in both groups were also asked to avoid food made of blood and vitamin C tablets. The time between preparation of smears and testing was less than 6 days in 96% of the subjects. The majority of the slides were smeared wet. The vast majority of the slides were developed and read by the same technician.

Individuals with one or more positive tests were called to the hospital for a workup, including a personal interview during which the doctor decided whether the subject had abdominal symptoms or not (asymptomatic and symptomatic, respectively). It was noted whether the subject had observed blood in the feces during the previous six months. A digital rectal examination, proctoscopy, and rectosigmoidoscopy with a flexible instru-

ment (60 cm) were performed after the interview. All subjects were then referred for a double-contrast enema (DCE) examination of the colon. Subjects with a negative workup for neoplasm or inflammatory bowel disease were asked to perform a second test series with three new Hemoccult II slides. Those with one or more positive tests were further examined by radiography of the stomach and by colonoscopy.

Second Screening

All subjects in the test group were offered rescreening 16 to 22 months (mean, 20) after the first study. The rescreening was started in April 1984 and completed in December 1985. Seven hundred forty-nine subjects died between the first and second screening, and the addresses of 22 subjects could not be found. The control and test groups consisted of 13,375 and 13,357 subjects, respectively at the start of the second screening. This screening was performed in the same way as the first one, but all slides were rehydrated before development. The subjects were asked to avoid fruit and vegetables 2 days before and during the sample collection as well as food made of blood and vitamin C tablets. The workup of subjects with a positive test was the same as in the first screening. Those who had been positive in the first screening and participated in the workup then, and were again positive in the second screening were called for colonoscopy without an ordinary workup in the second screening. No repeat Hemoccult tests, after a negative workup of an initial positive test, were done in the second screening.

Follow-Up

Follow-up of the whole study population is achieved by continuous quarterly contact with the local Cancer and Death Register, weekly contact with the three Departments of Surgery in the city of Göteborg, and continuous contact with the register at the Department of Pathology. Individuals leaving the area are continuously observed through the National Cancer Register. By these routines working through four different administrative channels, it should be virtually impossible for a person in our study with any diagnosed colorectal neoplasm to slip away from us.

All removed neoplasms have been examined by the same pathologist. The adenomas were measured before fixation. All new batches of Hemoccult II were evaluated at the Reference Laboratory for Fecal Occult Blood Testing, Memorial Sloan-Kettering Cancer Center, New York City, NY. The statistical calculations were performed using Fisher's exact test significance: $P < 0.01$.

TABLE 1. Comparative Data on Hydrated *Versus* Nonhydrated Slides in the First Screening Period

	No. of subjects	Positive tests		Complete workup	Neoplasms (true positive)	Positive predict value
Nonhydrated group	4436	84	1.9%	76	24	32%
Hydrated group	4604	256	5.8%	228	50	22%

Results

First Screening

Sixty-six percent of the 13,759 subjects completed both the test and the questionnaire, and 12% answered only the questionnaire. The compliance in terms of completed tests in the two subgroups with and without rehydration was 64 and 67%, respectively. Seventy-eight percent (7063) of all responders returned the completed tests after the first mailing, 15% (1393) after the first reminder letter, and 7% (584) after the second letter.

Of the subjects in the unrehydrated test group, 1.9% (84 of 4436) had positive tests compared to 5.8% (265 of 4604) of the subjects in the group where the slides were rehydrated before development. The rate of true positives and the positive predictive value in the two groups is shown in Table 1.

Three hundred four of the 349 subjects with a positive test series had a complete workup, 18 had a limited workup with proctoscopy and rectosigmoidoscopy, and 27 subjects refused workup. A new series of Hemocult II tests was done by 206 of the 224 subjects in whom the workup had not revealed any colorectal neoplasm or inflammatory bowel disease. The new Hemocult II test series was positive in 50 of these subjects (24%). Forty of these subjects underwent colonoscopy, and 43 had radiography of the stomach. One subject with carcinoma and five with adenoma were found at

colonoscopy to be among those with a positive Hemocult II at the repeat investigation. One polyp was found in a subject with unhydrated tests, and the other neoplasms were found in subjects with hydrated tests. Only one subject with a polyp has been diagnosed among the 156 subjects with a negative Hemocult II test. No neoplasm was found in those who refused to repeat the test. All radiographs of the stomach were normal.

The investigation of the 322 subjects with positive Hemocult II tests revealed neoplastic disease in 74 individuals, 16 with infiltrating carcinoma and 58 with altogether 75 adenomas, 43 of which were 1 cm or larger in diameter. Four of the subjects with carcinomas and 20 with adenomas belonged to the group where the slides were not rehydrated (Table 2).

Second Screening

The compliance rate in the second screening is shown in Table 3. Ninety-three percent of those who submitted the slides in the second screening had also performed the test on the first occasion, and 7% (524) were new in the second screening. One thousand seven hundred eighty-five of the subjects who had performed the test in the first screening and were alive did not participate in the second screening.

Eight percent (307 of 3820) positive Hemocult II tests were found in those who had belonged to the subgroup in which the slides were not rehydrated in the first

TABLE 2. The Number of Subjects With Diagnosed Neoplasms in the Test and Control Groups in the First and Second Screenings and During the Interval Between the Two Screenings

	First screening period		Interval carcinomas (mean, 20 mo)	Second screening period*		Total carcinomas
	No. of subjects	Carcinomas		No. of subjects	Carcinomas	
Unhydrated group	4436	4	14	3820	12	30
Rehydrated group	4604	12	2	3950	7	21
Nonresponders	4719	—	10	5587	—	10
Control group	13744	2	16	13375	2	20
			Adenomas			
Unhydrated group		20	4		59	83
Rehydrated group		38	1		32	71
Nonresponders		1	6		1	8
Control group		1	22		1	24

* The slides from all subjects in the second screening were rehydrated.

TABLE 3. Compliance in the First and Second Screenings

	No. of subjects	Performed Hemocult II plus questionnaire		Questionnaire only		Nonresponders	
		No.	Percent	No.	Percent	No.	Percent
First screening	13,759	9040	66	1687	12	3032	22
Second screening	13,357	7770	58	1897	14	3690	28

screening. Four point eight percent positive tests were found in those who belonged to the subgroup in which the Hemocult slides were rehydrated in the first screening. Four hundred thirty-five (88%) of those with a positive test had a full workup, 20 had a limited workup with proctoscopy and rectosigmoidoscopy, and 42 subjects refused workup. Twenty-five subjects with a positive test in the second screening also had a positive test in the first screening. All these subjects were offered and underwent a colonoscopy.

The investigation of the 455 subjects with a complete or limited workup during the second screening revealed neoplastic disease in 110 individuals (Table 2). Sixty-eight of 126 adenomas were one centimeter or larger in diameter.

Combined Results of First and Second Screening

Colorectal carcinomas were diagnosed in the interval between the two screening periods in 16 subjects with negative tests, in 14 in the unhydrated subgroup, and in two individuals in the rehydrated subgroup. Carcinomas were found during the same period in ten of the 4719 refusers who did not participate at all (Table 2). Altogether, 61 subjects with colorectal carcinomas were found in the screening group, and 20 subjects with colorectal carcinomas were found in the control group from the start of the first screening to the end of the second screening ($P < 0.001$, Table 2). The mean duration of this period was 27 months. The distribution of the carcinomas according to the Dukes classification in the two groups and among those in the test group who were

diagnosed with the aid of the Hemocult II test is shown in Table 4.

Carcinomas were overlooked in five subjects at the initial workup of a positive Hemocult II test. Three of them had a positive Hemocult II at the repeat test, and carcinomas were diagnosed in two subjects at the subsequent colonoscopy (Dukes A and C). The third repeatedly positive subject refused colonoscopy and returned due to symptoms caused by carcinoma 8 months later (Dukes D). The fourth subject had a negative Hemocult at the repeat test, and the fifth was not offered another test. In these two subjects the carcinomas in the cecum and the transverse colon, respectively, were overlooked at the radiographic examination. The subjects returned with symptoms caused by the tumor 27 and 28 months later (Dukes C and D), respectively.

The occurrence of abdominal symptoms that might be due to the diagnosed neoplasm and the presence of blood from the anus during a 6-month period before diagnosis are shown in Table 5. Only one of seven subjects with a carcinoma and abdominal symptoms had seen a doctor for these symptoms. This happened just before she was called for workup of the positive Hemocult II test.

Colorectal adenomas were diagnosed in 162 subjects in the test group and in 24 subjects in the control group ($P < 0.01$, Table 2). One hundred four and eleven, respectively, of these adenomas were one centimeter or larger in diameter ($P < 0.01$).

The number of diagnosed neoplasms in the rehydrated group at the first screening was significantly ($P < 0.01$) larger than in the unhydrated group. The number of subjects with a diagnosed neoplasm in the interval between the two screening periods as well as the number of diagnosed neoplasms in the second screening was, conversely, significantly greater ($P < 0.01$) in the unhydrated group (Table 6).

The diagnostic findings from the two screenings are shown in Table 7. Hemorrhoids were diagnosed at these times in 231 and 284 subjects, respectively. The hemorrhoids were considered to be a possible source of bleeding in 88 and 77 individuals, respectively, and a decision about possible bleeding in these subjects could not be made in 79 and 98 subjects, respectively. A probable

TABLE 4. Distribution of Carcinomas According to the Dukes Classification

Dukes	Diagnosed with Hemocult II*		Screening group		Control group	
	No.	Percent	No.	Percent	No.	Percent
A	12	34	13	21	3	15
B	8	23	15	25	5	25
C	11	32	22	36	7	35
D	4	11	11	18	5	25
Total	35	100	61	100	20	100

* Diagnosed with Hemocult II are those cases (35/61) in the screening group that were found with the aid of the Hemocult II test.

TABLE 5. Number of Clinically Asymptomatic Subjects With Neoplasm and the Number of Subjects Who Had Not Noticed Blood From the Anus Once or More During 6 Months Before Diagnosis

Tumor type	No. of subjects	No abdominal symptoms		No history of bleeding		No abdominal symptoms and no bleeding	
		No.	Percent	No.	Percent	No.	Percent
All adenomas	149	136	91	94	63	89	60
Adenomas \geq 1 cm	95	85	89	46	59	52	55
Carcinomas	35	28	80	16	46	15	43

source of bleeding was found in at least 48% (154) and 43% (197) of the worked-up subjects in the first and second screening, respectively. Diverticula were not looked upon as a source of bleeding.

Discussion

Rehydration of the Hemoccult II slide before development increases the sensitivity but decreases the specificity of the test. This means that rehydration considerably increases the work load as more subjects have to be investigated because of a false-positive test. However, if too many carcinomas are overlooked due to false-negative tests, screening will be worthless. The proportion of negative tests in subjects who were subsequently found to have a colorectal carcinoma was 72% in the subgroup with unhydrated tests. This figure is much higher than those previously reported but similar to that postulated by Simon.⁷ In the rehydrated group the number of subjects with carcinoma and a false-negative Hemoccult test was much lower (7%), as could be expected. Our results are thus in agreement with those obtained in the Minnesota study; *i.e.* Hemoccult II slides must be rehydrated before development.³ We could not confirm the claim that rehydration does not increase the diagnostic yield.⁸ If the slides are not rehydrated, the incidence of diagnosed colorectal carcinomas will be about the same as among the nonresponders. We therefore disagree with those who do not recommend rehydration of the Hemoccult II before development.^{8,9}

The increased sensitivity after rehydration means that the number of false-positive tests increases strongly as the specificity decreases. In order to reduce the number of false-positive tests after rehydration, it has been suggested that the subjects should keep to a low meat- and peroxidase-containing diet before and during the test period as such food can cause a false-positive test.^{10,11} However, Norfelt *et al.* could not show any effect on sensitivity or specificity of a red meat-free diet.¹² We do not know whether the dietary restrictions in our program had an impact on the number of false-positive tests. The rate of false-positive tests, here defined as the absence of neoplasms, was 71% and 83% in the unhy-

drated and rehydrated groups, respectively. Another way to reduce the number of false-positive tests might be to reexamine those with a positive rehydrated test and only investigate the subjects who are positive at the second testing.¹³

Strictly speaking, false-positive tests are only those that are positive due to other causes than blood as the guaiac test measures the presence of blood and not the presence of neoplasm. Only about half of the positive tests were found to be due to a possible source of bleeding when some of the diagnosed hemorrhoids, inflammatory bowel disease, and neoplasms were looked upon as possible sources. Diverticula in the colon were not considered a source.¹⁴ A blood-specific test like the Hemquant¹⁵ (Smith Kline Diagnostic, Sunnyvale, CA) might, therefore, possibly reduce the number of all positive tests to about half without decreasing the high sensitivity obtained with rehydrated Hemoccult II tests.

Screening for the early detection of colorectal cancer requires a considerable effort in order to reach a compliance of 68%. A great deal of effort is also needed to achieve a high compliance rate in the workup of those with a positive test. The population to be screened, therefore, has to be carefully selected in order to get the most benefit from the available resources. Screening with the guaiac test will always result in a number of false-positive tests, which means that the positive predictive value will decrease with decreasing incidence of neoplasms in the screened population.¹⁶ The incidence

TABLE 6. Number of Diagnosed Neoplasms in the Unhydrated and Rehydrated Groups in the First and Second Screening and During the Intervening Interval

	No. of subjects	First screening	Interval	Second screening*
Unhydrated group	4436	24	18	71
Rehydrated group	4604	50	3	39
		$P < 0.006$	$P < 0.001$	$P < 0.002$

* The slides from all subjects in the second screening were rehydrated before development.

TABLE 7. Diagnostic Findings in the Two Screenings in Subjects With a Positive Hemocult II Test

	No. of subjects examined for a positive Hemocult	Percent neoplasms	Percent inflammatory bowel disease	Percent hemorrhoids	Percent diverticula
First screening	322	24	3	72	41
Second screening	455	24	3	62	30

of colorectal cancer in individuals between 45 and 49 years of age is only 30% of that in individuals between 55 and 59 years of age and only 20% of that in individuals between 65 and 69 years of age.¹⁷ Forty-five years has generally been chosen as the age at which screening shall start, but no scientific evidence for this decision seems to exist.^{3,4} In our mind screening for colorectal cancer should start at the age of 55 as it seems likely that the diagnostic yield will thereby increase.

The diagnostic methods used in the workup of positive tests are important for the outcome of the screening program.¹⁸ Rectoscopy with a rigid instrument and barium enema is too unsatisfactory to be used. Colonoscopy is considered to be a necessity in the Minnesota study, while we consider double-contrast barium enema and rectosigmoidoscopy (60 cm) to be satisfactory for the examination.^{3,18} To our knowledge, there is no controlled study that has shown better results with colonoscopy. In the present study five carcinomas were overlooked. One of the overlooked carcinomas was diagnosed at colonoscopy performed as a consequence of a positive test at a repeat fecal examination and another was diagnosed at colonoscopy performed to remove a diagnosed adenoma. The other three carcinomas were diagnosed only as a result of the fact that they caused symptoms reputed by individuals.

We do not know how often and at what intervals the screening should be repeated in order to get the best results. According to our results, at least one rescreening within 12 to 20 months seems to be necessary when the slides are rehydrated as 30% of the carcinomas and about 50% of the adenomas were found at rescreening in this group. Whether a second rescreening is of any benefit is still unknown, but it might be possible to determine its value from the results of continued observation of our population.

The number of asymptomatic subjects with colorectal neoplasms varies with different screening materials.^{1,4,7} The relationship between individuals with and without gastrointestinal symptoms and a colorectal neoplasm in a screening material is important in the evaluation of the screening. This relationship most likely reflects the possible admixture of subjects who have been included as they have consulted for symptoms caused by a colorec-

tal neoplasm and not found by the screening procedure. In the present material 80% of the subjects with a diagnosed carcinoma and 91% of those with an adenoma had not noticed any abdominal symptoms. Some of these subjects had noticed bleeding from the anus within 6 months before the screening. However, bleeding in this age group is a rather unspecific symptom because no less than 12% reported that they had noticed blood from the anus one or more times during a 6-month period before the screening. Forty-three percent of the subjects with carcinomas and 60% of the subjects with an adenoma were clinically asymptomatic and had never noticed any bleeding.

The distribution of the diagnosed colorectal carcinomas according to the Dukes classification varies with different materials. Twelve of twenty diagnosed carcinomas in Hardcastle's material belonged to Dukes A.⁴ In a study in Germany about 70% of the carcinomas were of Dukes A or B type, and in the Minnesota study 61% of the carcinomas were classified as Dukes A or B.^{1,19} In this study there was no significant difference in the Dukes classification between the diagnosed carcinomas in the test and control group, although three times more carcinomas were diagnosed in the test group compared to the control group (61 and 20 carcinomas, respectively). If the staging of the carcinoma diagnosed with the aid of Hemocult II was compared with the carcinomas in the control group, there was a clear trend toward more favorable tumor staging in the test group. The reason for the discrepancy between this and other materials could be that only a little more than half of the carcinomas in the test group were diagnosed with the aid of the Hemocult II. Thus, 14 subjects with carcinomas had a false-negative test (13 in the unhydrated subgroup), the carcinomas were overlooked during the double-contrast enema in two individuals, and ten carcinomas were found among the nonresponders. All these carcinomas were diagnosed due to the subjects' symptoms. Another reason for the difference in Dukes classification between this and some other materials might be that all subjects but one with malignant adenomas had a large bowel resection. Surprisingly, two of these subjects had metastases to the lymph nodes. If these subjects had not been operated on, they would have been classified as

Dukes A instead of Dukes C. One must remember that Dukes classification is impossible to perform if the lymph nodes are not microscopically examined.

In order to get the best possible results with this method of screening, special attention must be paid to three factors: the sensitivity of the test, the compliance, and the sensitivity of the methods used for workup of a positive test. For the purpose of increasing the possibilities of obtaining an answer to these questions, the screening study has been increased to twice as many subjects (51,477). The second half of this study is in progress.

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