



## Evaluation of a fecal occult blood test with reverse passive hemagglutination for colorectal neoplasm screening

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### Abstract

**AIM:** To evaluate the one and three sampling reverse passive hemagglutination fecal occult blood test (RPHA FOBT) for colorectal neoplasm screening.

**METHODS:** A group of 3034 individuals with histories of colorectal polyps and/or ulcers were screened for colorectal cancer. Three day fecal samples were collected and 60 cm fiberoptic colonoscopy was conducted for each subject. The fecal samples were tested for occult blood with the RPHA method and the endoscopic and histopathological diagnoses were used as standard reference for evaluation. The sensitivity, specificity and positive and negative predictive values of different samplings were compared.

**RESULTS:** About 521 cases of colorectal neoplasms were detected, including 12 cases of colorectal cancer and 509 cases of polyps. Results showed that the mean sensitivity of one sampling RPHA FOBT for colorectal neoplasm was only 13.2%, the specificity was 90.3% and the positive and negative predictive values were 21.3% and 83.4%, respectively; while for the three sampling, taking one positivity as positive, the sensitivity increased to 22.0%, the specificity decreased to 81.6% and the positive and negative predictive values were 19.7% and 83.6%, respectively.

**CONCLUSION:** A single RPHA FOBT seems to be less sensitive for screening for colorectal neoplasms. Since it is convenient and economical, RPHA FOBT remains the most practical procedure for detection of early colorectal cancer and polyps if it is combined with other screening methods.

**Key words:** Colonic neoplasms; Rectal neoplasms; Colonic polyps; Hemagglutination tests; Occult blood

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### INTRODUCTION

Fecal occult blood test (FOBT) has been the most important procedure for population screening for colorectal cancer since Greigor first reported it in 1967<sup>[1,2]</sup>. During screening, both early colorectal cancer and precancerous lesions such as adenomatous polyps can be detected, so screening for colorectal neoplasms with FOBT is a procedure of secondary prevention as well as a measure for primary prevention of colorectal cancer. The conventional chemical FOBT (e.g. hemoccult) requires dietary control to reduce the false positive rate and the three day sampling to reduce the false negative rate. Although the reverse passive hemagglutination (RPHA) method which was developed in the 1980s raised the sensitivity and specificity of screening, Saito *et al*<sup>[3]</sup> suggested that a single sampling RPHA may be adequate for screening. This has not been verified in large population screening. In the present study, we screened a high risk population for colorectal cancer with RPHA FOBT and 60 cm fiberoptic colonoscopy and evaluated various protocols of RPHA FOBT (one, two and three sampling) for screening for colorectal neoplasms.

### MATERIALS AND METHODS

#### Subjects

A total of 3034 individuals with a history of rectal polyps and ulcers detected in mass screening 10 years ago in Haining and Jiashan counties in Zhejiang province included 1716 males and 1318 females, aged 32-72, with a mean age of 49.2 years.

#### Methods

All subjects had a 60 cm fiberoptic colonoscopy and those with positive endoscopic findings had a biopsy for histopathological examination. The bowel preparation and endoscopic procedures were reported in another paper<sup>[4]</sup>. No dietary control was required and three day fecal samples were collected and submitted for laboratory testing before endoscopy. The RPHA FOBT was performed for each sample, according to Zhu *et al*<sup>[5]</sup>. During analysis, subjects were divided into two groups: Neoplasm (cancer, adenoma

**Table 1 Relationship between the 1<sup>st</sup> reverse passive hemagglutination fecal occult blood test and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	60	250	310
	-	380	1863	2243
Total		440	2113	2553

Sensitivity: 13.6% (60/440), specificity: 88.2% (1863/2113), positive predictive value: 16.1% (60/310), negative predictive value: 83.1% (1863/2243).

**Table 2 Relationship between the 2<sup>nd</sup> reverse passive hemagglutination fecal occult blood test and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	50	168	236
	-	372	1823	2195
Total		422	2009	2431

Sensitivity: 11.8% (50/422), specificity: 90.7% (1823/2009), positive predictive value: 21.2% (50/236), negative predictive value: 83.1% (1823/2195).

**Table 3 Relationship between the 3<sup>rd</sup> reverse passive hemagglutination fecal occult blood test and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	55	151	206
	-	333	1733	2066
Total		388	1884	2272

Sensitivity: 14.2% (55/388), specificity: 92.0% (1733/1884), positive predictive value: 26.7% (55/206), negative predictive value: 83.9% (1773/2066).

and polyps) and non neoplasm, according to endoscopic and histopathological diagnoses. For those who completed three RPHA FOBT, three test thresholds were used: (1) all tests positive as positive [3/3 (+)]; (2) two positive as positive [2/3 (+)]; and (3) one positive as positive [1/3 (+)]. The sensitivity, specificity and positive and negative predictive values were used as efficacy indicators for evaluation. For comparison,  $\chi^2$  test was performed with Epi info software and the Mantel Haenszel or Yate's correction was used for significance analysis.

## RESULTS

Out of 3034 subjects, 521 cases of colorectal neoplasms were diagnosed by endoscopic and histopathological examination. There were 12 cases of cancer and 509 polyps, in which adenoma accounted for 45.0% (229/509). Among 2553 subjects who completed at least one FOB test, there were 440 neoplasias (12 cancers and 428 polyps); in 2431 subjects who had at least 2 FOB tests, there were 422 neoplasias (12 cancers and 410 polyps); in 2272 subjects who completed three FOB tests, 388 cases of neoplasia were detected, including 11 cancers and 377 polyps. The correlation between neoplasia and three FOBT results is presented in Tables 1-3. The mean sensitivity, specificity and positive and negative predictive values for three tests were 13.2%, 90.3%, 21.3% and 83.4%, respectively. In 2272 subjects who had three FOB tests, the sensitivity and specificity of the FOB test to neoplasia using different positive thresholds are shown in Table 4, Table 5 and Table 6. It was demonstrated that with the elevation of a positive threshold [1/3 (+) to 3/3 (+)], the sensitivity decreased from 22.0% to only 5.4%, while the specificity increased from 81.6% to 96.5%.

## DISCUSSION

Occult bleeding of the lower digestive tract is the most common symptom of early cancer or polyps of the large bowel. Meanwhile, in physiological conditions, there can be a small amount of bleeding

**Table 4 Relationship between three sampling 1/3 (+) and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	85	346	431
	-	302	1539	1841
Total		387	1885	2272

Sensitivity: 22.0% (85/387), specificity: 81.6% (1539/1885), positive predictive value: 19.7% (85/431), negative predictive value: 83.6% (1539/1841).

**Table 5 Relationship between three sampling 2/3 (+) and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	46	138	184
	-	341	1747	2088
Total		387	1885	2272

Sensitivity: 11.9% (46/341), specificity: 92.7% (1747/1885), positive predictive value: 25.0% (46/184), negative predictive value: 83.7% (1747/2088).

**Table 6 Relationship between three sampling 3/3 (+) and colorectal neoplasm**

		Colorectal neoplasm		Total
		+	-	
RPHA FOBT	+	21	66	87
	-	366	1819	2185
Total		387	1885	2272

Sensitivity: 5.4% (21/387), specificity: 96.5% (1819/1885), positive predictive value: 24.1% (21/87), negative predictive value: 83.2% (1819/2185)

in an apparently normal digestive tract; it is, however, seldom more than 2 mL over 24 h. The conventional chemical FOB test has a low sensitivity and can only detect more than 10 mL/24 h of bleeding in the lower digestive tract<sup>[6]</sup>. Therefore, a three day sampling has been recommended clinically to elevate the sensitivity of the test. However, it is difficult to implement in large population screening because of the greatly increased work load of sample collection, lab tests, the data process and the cost for reagents. In 1984, Saito first reported the application of RPHA FOBT in screening colorectal cancer, suggesting that one sampling RPHA might replace the three day hemoccult test<sup>[3]</sup> because the former had a higher sensitivity. In China, Zhou *et al*<sup>[7]</sup> also successfully developed RPHA FOB test kits that can detect intestinal bleeding as small as 0.48 mL/24 h.

In order to objectively evaluate the efficacy of RPHA in screening for colorectal neoplasias, the present study compared the results of one with three sampling RPHA FOBT, using 60 cm fiberoptic colonoscopy as a standard reference. Our study revealed that the mean sensitivity of one sampling RPHA FOBT was only 13.2%, which means that as many as 86.8% of colorectal neoplasias might be missed if FOBT is used as the only measure for screening. However, when the three sampling method is used with taking 1/3 (+) as positive criteria, 22.0% of colorectal neoplasias can be detected. The authors previously reported that the sensitivity of three sampling RPHA FOBT for colorectal cancer was 63.6% and was 40% for villous or tubulovillous adenoma, which has an increasing tendency to malignant transformation<sup>[8]</sup>.

The low sensitivity of one sampling RPHA FOBT may result from the variation of bleeding status of early colorectal neoplasia, particularly polyps. Ahlquist *et al*<sup>[9]</sup> measured FOB with a hemoccult test consecutively for 2 wk in a group of patients with colorectal cancer. They found that only one quarter of the patients presented with consistent positivity and that the FOB fluctuated day by day in the remainder. Therefore, three day sampling is more likely to find occult intestinal bleeding; on the other hand, it will definitely increase the cost and work load of screening, particularly in a large population. To cope with this dilemma, we designed a new screening protocol comprising one sampling RPHA FOBT plus a computerized

risk assessment as a primary screening procedure. With the combination of two methods, the sensitivity of primary screening will be raised. In a high incidence area, we screened 62, 667 individuals aged 30 and above using this protocol. Among them, 4299 subjects required endoscopic examination; in 3162 people who underwent endoscopy, 397 cases of colorectal neoplasia were detected, including 41 cancers and 356 polyps. In all cases of neoplasia, 172 (43.3%) had a positive FOBT and the remaining 56.7% of cases were screened endoscopically only according to risk assessment<sup>[10]</sup>. In conclusion, RPHA FOBT is a convenient, economical and noninvasive method for screening colorectal neoplasia, although it is less sensitive. If used in combination with other screening measures, RPHA FOBT can still be an effective method for detecting early colorectal cancer and polyps. Whether to choose one or three sampling methods depends on the size of the screened population and the availability of resources.

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