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Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer

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Abstract

This study was carried out to assess, from the aspects of cost-effectiveness and diagnostic validity, the optimum cut-off point for immunochemical occult blood testing using a 2-day method as a means of screening for colorectal cancer. Four thousand, two hundred and sixty asymptomatic individuals were subjects of this study. They gave samples for an immunochemical fecal occult blood test, and colonoscopy was carried out during a medical check-up. For evaluation of the optimum cut-off point, three cut-off levels of fecal haemoglobin, 50, 150 and 300 ng/ml, were used. A total of 27 patients with colorectal cancer were diagnosed. The average costs to detect one patient with colorectal cancer and the sensitivity and specificity of these three cut-off points of fecal haemoglobin were evaluated. The average costs for the detection of one cancer case were calculated as $2870.45 for cut-off level of 50 ng/ml, $2492.98 for that of 150 ng/ml and $3329.09 for that of 300 ng/ml, respectively. The sensitivity and specificity were calculated as 89 and 94% for the 50 ng/ml cut-off level, 81% and 96% for the 150 ng/ml cut-off level and 56 and 97% for the 300 ng/ml cut-off level, respectively, indicating a significant difference in the sensitivity between the 50 and 300 ng/ml levels ($P < 0.05$), as well as between the 150 and 300 ng/ml levels ($P < 0.05$), and a significant difference in the specificity between the 50 and 300 ng/ml levels ($P < 0.05$). However, no significant difference was observed in the specificity between the 50 and 150 ng/ml levels. The findings show that 150 ng/ml of fecal haemoglobin is the optimal cut-off point when carrying out the OC-Hemodia test as a means of screening for colorectal cancer.

Keywords: Colonoscopy; Cost-effectiveness; Cut-off point; Fecal haemoglobin; Immunochemical occult blood test

1. Introduction

Currently in Japan, the immunochemical fecal occult blood test has been widely used for the early detection of colorectal cancer. In a previous study, we demonstrated that an immunochemical test was more accurate in detecting cancer than a chemical guaiac test [1]. A wide variety of commercially immunochemical tests are now available, including the latex agglutination tests, the reversed passive haemagglutination tests, the latex agglutination inhibition tests, the enzyme-linked immunosorbent assay (ELISA), the fluorescence enzyme immunoassay, the gold-coloric method and the immunocolorific method. Several reports using these tests have demonstrated the usefulness of the immunochemical occult blood tests as a method for colorectal cancer screening [2–7].

The costs of these immunochemical occult blood tests, however, are slightly more expensive than the guaiac-based chemical occult blood test, Hemoccult II [8], which has been the primary test used in screening programmes for colorectal cancer in Western countries [9–11]. Accordingly, in large-scale population screening for colorectal cancer by the immunochemical occult blood test, special attention should be paid to the number of fecal specimens collected from the economic aspect. In a previous investigation [12], we reported that a two-day fecal collection method was optimum for an immunochemical occult blood screening from the viewpoint of cost-effectiveness.

High diagnostic validity, on the other hand, is essential for a cancer screening test, and the sensitivity and specificity are directly influenced by the cut-off level. However, little information is available on the optimum cut-off point in order to balance an appropriate screen-

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Table 1
Age and sex distribution of the subjects

	Sex			
Age (years)	Male	Female	Total	Male/Female
40–49	546	610	1156	0.90
50–59	742	785	1527	0.95
60–69	421	509	930	0.83
70+	270	377	647	0.72
Total	1979	2281	4260	0.87

ing test with optimal cost-effectiveness and a high diagnostic validity. In this study, we evaluated the optimum cut-off point of the immunochemical occult blood test, OC-Hemodia, through the comparison of the average costs required to detect one colorectal cancer case using three cut-off points.

2. Patients and methods

Four thousand, two hundred and sixty asymptomatic people aged over 40 years who participated in a medical check-up for colorectal cancer between April 1990 and March 1999 served as subjects of this study. Their age and sex distributions are listed in Table 1. The percentage of the participants with a family history of colorectal cancer was 15.5% (661/4260). The four samples of two consecutive days stool from each subject were tested by an immunochemical fecal occult blood test, OC-Hemodia, without dietary or medicinal restriction according to the test principle before conducting colonoscopy. Fecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received a colonoscopic examination.

For the evaluation of the average costs for the detection of one colorectal cancer case, we initially used five cut-off points and following an analysis of the no of cancers detected (data not shown) this was reduced to three cut-off points of fecal haemoglobin, 50, 15 and 300 ng/ml. These were determined using an immunochemical test where the agglutinated haemoglobin/polystyrene latex complex is measured at 660 nm with an OC-sensor analyser. The costs of the immunochemical occult blood test, as well as the colonoscopic procedure, were also calculated. In addition, the diagnostic accuracies were compared for these three cut-off points of fecal haemoglobin.

The principles and procedures of the immunological slide, OC-Hemodia (a latex agglutination test), which was used in the present study, are as follows. Those being examined are asked to pierce the point of a collection stick into the fecal sample in several different places, then to seal up the point in a tube containing ammonium buffer liquid. Two drops from the liquid containing the fecal samples in the plastic tube are put in round wells and mixed with an anti-human haemoglobin antibody that is attached to polystyrene latex particles. The absorbance of the agglutinated haemoglobin/polystyrene latex complex is measured at 660 nm with an OC-sensor analyser. The procedures of this commercial test are not complicated and are performed in a hospital laboratory or a physician's office. In addition, the procedure does not require a specially trained individual to perform it or to evaluate the test results. The manufacturer's price per slide for each test is approximately \$3.64 (¥400).

Statistical analysis was performed by McNemar's test and a two-tailed P value of less than 0.05 was defined as being statistically significant.

3. Results

Twenty-seven patients with colorectal cancer were diagnosed by colonoscopy. Among them, 15 patients had Dukes' A cancer, and Dukes' B, C and D cancer was diagnosed in 8, 3 and 1 patient, respectively. Positive cases of an immunochemical fecal occult blood test were 278 (6.5%), 175 (4.1%) and 139 (3.3%) using the 50, 150 and 300 ng/ml cut-off levels. The number of patients with colorectal cancer detected by the fecal occult blood test were 24, 22 and 15 using the 50, 150 and 300 ng/ml cut-off levels.

The average costs for the detection of one cancer case were calculated as \$2870.45 for the cut-off point of 50 ng/ml, \$2492.98 for the 150 ng/ml level and \$3329.09 for the 300 ng/ml level, respectively (Table 2). Colonoscopy revealed three false-negatives and 254 false-positives using the 50 ng/ml level, five false-negatives and 153 false-positives using the 150 ng/ml level and 12 false-negatives and 124 false-positives using the 300 ng/ml level. Accordingly, the sensitivity and specificity were calculated as 24/27 (89%) and 3979/4233 (94%) for the 50 ng/ml level, 22/27 (81%) and 4080/4233 (96%) for the 150 ng/ml level and 15/27 (56%) and 4109/4233 (97%) for the 300 ng/ml level, respectively, indicating a significant difference in the sensitivity between the 50 and 300 ng/ml levels ($P < 0.05$) as well as between the 150 and 300 ng/ml levels ($P < 0.05$), and a significant difference in the specificity between the 50 and 300 ng/ml levels ($P < 0.05$). However, no significant difference was observed in the specificity between the 50 and 150 ng/ml levels. The number of adenomatous polyps detected $\geqslant 1$ cm and $\leqslant 1$ cm by colonoscopy for the three cut-off levels are shown in Table 3.

4. Discussion

The average costs and the sensitivity and specificity calculated in this investigation indicate that the cut-off

Table 2
Comparisons of the average costs per patient with colorectal cancer detected for the three cut-off points of fecal haemoglobin in the immunochemical fecal occult blood screening

	Cut-off points		
	50 ng/ml	150 ng/ml	300 ng/ml
I. Screening costs (A×B)	$30981.82	$30981.82	$30981.82
A. Fecal occult blood test	$7.27 (¥800)	$7.27 (¥800)	$7.27 (¥800)
B. No. of patients screened	4260	4260	4260
II. Examination costs (A×B)	$37909.09	$23863.64	$18954.55
A. Diagnostic examination	$136.4 (¥15000)	$136.4 (¥15000)	$136.4 (¥15000)
B. No. of patients examined	278	175	139
III. Total costs (I + II)	$68890.91	$54845.46	$49936.37
IV. No. of cancers detected	24	22	15
V. Average costs per case detected (III/IV)	$2870.45	$2492.98	$3329.09

point of 150 ng/ml fecal haemoglobin is recommended as the optimal cost-effective approach for the immunochemical fecal occult blood screening by OC-Hemodia, from the aspects of cost-effectiveness, as well as diagnostic accuracy.

Our findings should be interpreted with caution due to limitations in the study design. In cost-effectiveness analyses of screening programmes for cancer, there are many direct, indirect and intangible costs, such as screening, diagnosis, treatment, and non-medical costs or additional costs [13–16]. Because indirect and intangible costs are not easy to measure, their incorporation into economic evaluations remains controversial [16]. Thus, we limited the cost analysis to the fecal occult blood test and colonoscopic procedure for the subjects with positive results in the fecal occult blood test. However, future efforts should be concentrated on an overall evaluation of cost-effectiveness that includes the many indirect and ntangible aspects, such as the cost of treating complications of screening tests, the costs of the initial treatment for cancer and polyps, the costs of follow-up for cancer patients, and the terminal care costs.

Although two studies in Japan suggest that the immunochemical fecal occult blood test followed by colonoscopy is the most cost-effective screening test for colorectal cancer [17,18], the results of cost-effectiveness analyses of cancer screening usually depend on the incidence of cancer, which varies among countries. In addition, it depends on the technical minutiae of the specific test circumstances. For example, the costs of the endoscopic procedure differs among different countries and thus in some countries differing average costs would be obtained. Accordingly, cost-effectiveness analyses can not usually be generalised across different countries and studies.

The most desirable method to assess the diagnostic accuracy of a screening test is to conduct both a screening test and a close examination of all asymptomatic subjects in the community. However, the feasibility of carrying out such a study on a largescale is poor owing to the operational difficulties and ethical problems. Thus, a cross-sectional study in the hospital such as that employed here is recommended as the best alternative to investigate the accuracy of a screening test. The present study also provides information about the accuracy of a screening test, but has obvious limitations compared with the above-mentioned population-based study.

One of the common problems with several fecal occult blood tests, including chemical as well as immunochemical tests, is the interobserver and intra-observer variability in the interpretation of the test results. Partial or total automation of the development procedures provides a better standardisation of results. In addition, simpler procedures would increase the cost-effectiveness of screening and the compliance of the technician with the test. OC-Hemodia is simple and standardisation of the results is ensured, provided that the procedure is fully automated. It can be developed in an hour, and laboratory staff are not required to be continuously involved.

Table 3

No. of cases of adenomatous polyps $\geqslant$ 1 cm cases detected by colonoscopy	56
A. Cut-off point of 50 ng/ml fecal haemoglobin (sensitivity)	33 (59%)
B. Cut-off point of 150 ng/ml fecal haemoglobin (sensitivity)	30 (54%)
C. Cut-off point of 300 ng/ml fecal haemoglobin (sensitivity)	12 (21%)
No. of cases of adenomatous polyps < 1 cm detected by colonoscopy	162
A. Cut-off point of 50 ng/ml fecal haemoglobin (sensitivity)	36 (22%)
B. Cut-off point of 150 ng/ml fecal haemoglobin (sensitivity)	29 (18%)
C. Cut-off point of 300 ng/ml fecal haemoglobin (sensitivity)	18 (11%)

The costs of population screening are strongly influenced by the compliance rate. It might be predicted that colorectal cancer screening with a 2-day method by an immunochemical test would increase compliance as there is no dietary or medicinal restriction and a shorter period is required for fecal collection. In the general population, the cancer detection rate would be lower and the costs per cancer detected would therefore be higher if the participation rate in screening is low. With a higher compliance, however, the costs for each screened subject or each detected cancer would be lower.

In conclusion, our results indicate that the cut-off point of 150 ng/ml fecal haemoglobin is recommended for immunochemical fecal occult blood screening by OC-Hemodia, from the viewpoints of cost-effectiveness, as well as diagnostic validity.

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