



# A cost-effective analysis of the optimum number of stool specimens collected for immunochemical occult blood screening for colorectal cancer

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## Abstract

This study was carried out to assess, from the viewpoint of cost-effectiveness, the optimum number of faecal specimens to collect for use in immunochemical occult blood testing as a means of screening for colorectal cancer. 3300 asymptomatic individuals were subjects of this study. They gave samples for an immunochemical faecal occult blood test, monohaem and colonoscopy was carried out during a medical check-up. For evaluation of the optimum number of sampling specimens, the results of the first day of sampling, those of the first and second days, and those of samples taken for 3 consecutive days were considered as the single-day method, the 2-day method and the 3-day method respectively. The average cost to detect 1 patient with colorectal cancer, the detection rate and the false-positive rate of these three faecal sample collection methods were evaluated. The average costs for one cancer case detected were calculated as \$3630.68 for the single-day method, \$3350.65 for the 2-day method and \$4136.36 for the 3-day method, respectively. The detection rate and the false-positive rate were calculated as 47 and 3.5% for the single-day method, 82 and 4.7% for the 2-day method and 88 and 5.3% for the 3-day method, respectively. This detection rate was significantly different between the single- and the 2-day methods, as well as between the single- and the 3-day methods ( $P < 0.05$ ). No significant differences in the false-positive rate amongst the three testing methods were observed. This analysis suggests that a 2-day faecal collection method is recommended for immunochemical occult blood screening by Monohaem from the aspects of cost-effectiveness and diagnostic accuracy. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** Colonoscopy; Cost-effectiveness; Immunochemical faecal occult blood screening; Sample collection method

## 1. Introduction

The diagnostic accuracy of the faecal occult blood test for colorectal neoplasms is influenced by the number of faecal specimens and collection on 3 consecutive days is the generally accepted method for the guaiac-impregnated chemical faecal occult blood test [1–3]. Sensitivity of chemical tests with 3 consecutive days of collection has ranged from 26 to 95% in patients with symptomatic colorectal cancer [4–6].

The immunochemical faecal occult blood test for human haemoglobin was developed in an attempt to improve the performance of the guaiac-impregnated chemical faecal occult blood test, and has been demonstrated to have a higher level of sensitivity for colorectal

bleeding than the guaiac-based occult blood test [7–9]. In a previous study [10], we also reported that the diagnostic accuracy for colorectal cancer was higher in the immunochemical test, Monohaem, than in the widely used chemical guaiac-based test, Haemoccult II.

The costs of these immunochemical tests are slightly more expensive than the guaiac-impregnated chemical test [9,10]. Consequently, in large-scale screening programmes for colorectal cancer by the immunochemical occult blood test, special attention should be paid to the number of faecal specimens collected from the viewpoint of cost-effectiveness.

However, in the immunochemical faecal occult blood test, there is no clear understanding on the best number of faecal specimens to be collected in order to balance an appropriate screening test with optimal cost-effectiveness and a high accuracy. For this reason, we conducted a comparative study to evaluate the desirable number of faecal specimens using an immunochemical faecal occult blood test, Monohaem.

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## 2. Patients and methods

3300 asymptomatic people aged over 40 years of age who participated in a medical check-up for colorectal cancer served as subjects of this study. The six samples of 3 consecutive days' stool from each subject were tested by an immunochemical faecal occult blood, Monohaem, without dietary or medicinal restriction according to the test principle before conducting colonoscopy. Faecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received colonoscopic examination.

For the evaluation of the average costs per detection of one colorectal cancer case amongst the three faecal sample collection methods, we used the results of the first day to denote a single-day faecal collection method, the results of the first and second days as a 2-day faecal collection method and the results of the 3 consecutive days as a 3-day faecal collection method. The costs of the immunochemical occult blood test as well as colonoscopy procedure were also calculated. In addition, the accuracy of the diagnosis was compared for these three faecal collection methods.

The principles and procedures of the immunological slide Monohaem (Nihon Pharmaceutical, Japan), which was used in the present study, are as follows: firstly, those being screened are asked to make a thin faecal smear on the test filter paper. If human haemoglobin is present in the faecal sample, an antigen–antibody reaction will occur with the monoclonal antibody in the filter paper. The reacted sample is then washed to remove components other than the haemoglobin and a colour coupler is added. Oxygen is dissociated from hydrogen peroxide by the peroxidase-like activity of the human haemoglobin, which oxidises tetramethylbenzidine, leading to the subsequent appearance of a green colour. The presence of human haemoglobin is thus indicated by the appearance of this green coloration. The procedures of this test are uncomplicated and the cost per slide for each test was ¥400 (Japanese Yen), equivalent to approximately US\$3.64. The cost of colonoscopic examination for one person was ¥15 000, equivalent to approximately US\$136.36 (according to the exchange rate of US\$1.00 = ¥110 during the period of check-up).

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

## 3. Results

17 patients with colorectal cancer were diagnosed by colonoscopy. Positive cases of an immunochemical faecal occult blood test were 125 (3.8%), 168 (5.1%), and 191 (5.8%) in the single-day, 2-day and 3-day methods.

Table 1

Results of immunochemical faecal occult blood testing and colonoscopy

|  |            |
|--|------------|
| I. No. of examinees                                  | 3300       |
| II. No. of positive occult blood cases (II/I)        | 191 (5.8%) |
| Single-day method                                    | 125 (3.8%) |
| 2-day method   | 168 (5.1%) |
| 3-day method   | 191 (5.8%) |
| III. No. of detected cancer (III/I) (by colonoscopy) | 17 (0.5%)  |
| Single-day method                                    | 8 (0.2%)   |
| 2-day method   | 14 (0.4%)  |
| 3-day method   | 15 (0.5%)  |

The number of patients with colorectal cancer detected by colonoscopic examination were 8, 14 and 15 in the single-day, 2-day and 3-day methods (Table 1). In the 17 patients where colorectal cancer was detected there were 10 cases of Dukes stage A (59%), 6 cases of Dukes stage B (35%) and 1 case of Dukes stage C (6%). Lesion sites included 3 in rectum (18%), 8 in sigmoid colon (47%), 3 in transverse colon (18%) and 3 in ascending colon (18%).

The costs of the immunochemical faecal occult blood test and colonoscopy as well as the average costs per case detected are shown in Table 2. The costs of colonoscopy in Table 2 were calculated for all positive subjects of faecal occult blood test.

Colonoscopy revealed 9 false-negatives and 117 false-positives in the single-day method, 3 false-negatives and 154 false-positives in the 2-day method and 2 false-negatives and 176 false-positives in the 3-day method (Table 3). Accordingly, the detection rate and the false-positive rate were calculated as 47 and 3.5% for the single-day method of collection, 82 and 4.7% for the 2-day method and 88 and 5.3% for the 3-day method, respectively. Thus, there were significant differences in the detection rate between the single- and 2-day methods ( $P < 0.05$ ) and between the single- and 3-day methods ( $P < 0.05$ ). No significant differences in the false-positive rates were observed for the three faecal collection methods (i.e. single-day versus 3-day method,  $P = 0.07$ ).

## 4. Discussion

Cost-effectiveness analyses aim to evaluate the net cost of providing a service and also to measure the outcomes obtained. The method commonly used is to calculate the cost per specified health effect of a technology in a programme, for example, costs per life year gained or costs per case identified and compare this cost-effectiveness ratio with the ratios from other interventions. It is a common understanding that the lower the ratio, the more 'cost-effective' the intervention. In

Table 2

Comparisons of average costs per patient with colorectal cancer detected for the three faecal collection methods of immunochemical faecal occult blood screening

|   | Faecal collection methods |                    |                    |
|---|---------------------------|--------------------|--------------------|
|   | Single-day                | 2-day              | 3-day              |
| I. Screening costs (A×B)                    | \$12 000.00               | \$24 000.00        | \$36 000.00        |
| A. Faecal occult blood test                 | \$3.64 (¥400)             | \$7.27 (¥800)      | \$10.91 (¥1200)    |
| B. No. of patients screened                 | 3300                      | 3300               | 3300               |
| II. Examination costs (A×B)                 | \$17 045.45               | \$22 909.09        | \$26 045.45        |
| A. Diagnostic examination                   | \$136.36 (¥15 000)        | \$136.36 (¥15 000) | \$136.36 (¥15 000) |
| B. No. of patients examined                 | 125                       | 168                | 191                |
| III. Total costs (I + II)                   | \$29 045.45               | \$46 909.09        | \$62 045.45        |
| IV. No. of detected cancers                 | 8                         | 14                 | 15                 |
| V. Average costs per case detected (III/IV) | \$3630.68                 | \$3350.65          | \$4136.36          |

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 [11–15].

In this study, in an attempt to clarify the optimum number of times to collect stool specimens, we limited the components of the costs to the faecal occult blood test, and colonoscopy procedure for the positive subjects of the faecal occult blood test. The average costs calculated in this study show that the 2-day testing method is the least expensive (\$3350.65) and is, therefore, recommended as the optimum cost-effective approach for immunochemical occult blood screening by Monohaem.

Physiological gastrointestinal bleeding has been estimated to be  $0.32 \pm 0.09$  mg/g stool [16] and 0.1–0.2 mg/g stool [17]. The lower the threshold value of the immunochemical faecal occult blood test, the higher the number of positive cases that will be detected in the actual screening. In the immunochemical test, Monohaem, for human haemoglobin employed in this study, a high antibody titre with the cut-off point 0.02 mg/g stool is used. Accordingly, the positivity rate of 5.1% in the 2-day method is higher than that of the guaiac-impregnated Hemoccult test [10], and a large proportion of the screened population will have a positive test result

following their annual screening. A higher positive rate in the faecal occult blood test increases cancer detection, but it also increases false-positive cases detected in the colonoscopic examination. This high positivity rate is a serious limiting factor for widescale screening of colorectal cancer and reconsideration of the threshold value of this test might be necessary as a trade-off between sensitivity and specificity.

The value obtained for the average costs per case is affected by the accuracy of the immunochemical occult blood test. Sensitivity analysis determines the degree to which uncertainty surrounding the costs and outcomes in the model affects the conclusion of the analysis. In this analysis, critical parameters, both costs and health outcomes, are varied over a broad range to determine if the preferred strategy changes. The detection rates in this study were evaluated as 47% in the single-day method, 82% in the 2-day method and 88% in the 3-day method, indicating a significant difference in the test sensitivity between the single- and 2-day method and between the single- and 3-day method. However, there were no significant differences in the detection rates and false-positive rates between the 2-day and 3-day methods. The cost of the 2-day method for one case of colorectal cancer identified was substantially lower than that of the 3-day method (US\$3350.65 versus US\$4136.36).

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

Table 3

Results of immunochemical faecal occult blood screening for colorectal cancer for the three faecal collection methods

| Colorectal cancer | Faecal collection methods |      |       |       |      |       |       |      |       |
|-------------------|---------------------------|------|-------|-------|------|-------|-------|------|-------|
|                   | Single-day                |      |       | 2-day |      |       | 3-day |      |       |
|                   | +                         | –    | Total | +     | –    | Total | +     | –    | Total |
| +                 | 8                         | 9    | 17    | 14    | 3    | 17    | 15    | 2    | 17    |
| –                 | 117                       | 3166 | 3283  | 154   | 3129 | 3283  | 176   | 3107 | 3283  |
| Total             | 125                       | 3175 | 3300  | 168   | 3132 | 3300  | 191   | 3109 | 3300  |

In terms of the cost-effectiveness of the immunochemical occult blood screening, a comparative study between the immunochemical and chemical tests shows that the average costs required to detect one colorectal cancer case by an immunochemical faecal occult blood test, the Monohaem method, is one-third lower than those by the guaiac-impregnated Haemoccult II test [18]. In addition, two studies in Japan suggest that the immunochemical faecal occult test followed by colonoscopy is most cost-effective in screening for colorectal cancer [19,20]. One note of caution should be added; this comparison may not always be valid since the cost of colonoscopy differs amongst different countries and thus in some countries differing average costs would be obtained. Indeed, the cost-effectiveness of immunochemical versus guaiac-based screening cannot usually be generalised across different studies and countries as it depends on the technical minutiae of the specific test circumstances.

In conclusion, the present economic analysis suggests that the 2-day faecal collection method described herein is the optimum procedure when carrying out the Monohaem test as a means of screening for colorectal cancer. To reconfirm the findings of the present study, however, it would be necessary to conduct a larger population-based prospective study using appropriate methods.

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