Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups

Yi-Yuan Chen a, Tsung-Hsing Chen a,b, Ming-Yao Su a,b, Hsiao-Chen Ning c, Chia-Jung Kuo a,b, Wei-Pin Lin a,b, Yu-Pin Ho a,b, Chun-Jung Lin a,b, Chen-Ming Hsu a,b,* Cheng-Tang Chiu a,b, Pang-Chi Chen a,b

a Department of Gastroenterology and Hepatology, Linkou Chang Gung Memorial Hospital, Gueishan, Taiwan
b Chang-Gung University, College of Medicine, Taoyuan, Taiwan
c Department of Clinical Pathology, Linkou Chang Gung Memorial Hospital, Gueishan, Taiwan

Received 17 April 2013; accepted 17 September 2013
Available online 12 July 2014

KEYWORDS
Colonoscopy; Colorectal cancer; Fecal occult blood test; Screening

Summary Background: In Taiwan, the prevalence of colorectal cancer has been increasing in recent decades. As a result, the fecal occult blood test (FOBT) has been advocated and widely used for colorectal cancer screening in areas with limited colonoscopy capacity. The goal of this study was to analyze the sensitivity of a single immunochemical FOBT (I-FOBT) and correlate it with the results of colonoscopy for detecting colorectal neoplasia in the asymptomatic Taiwanese population.

Methods: Data were collected from the results of health examinations conducted on asymptomatic adults older than 40 years and who simultaneously underwent one-time I-FOBT and colonoscopy examinations between January 01, 2008 and June 30, 2009. The sensitivity and specificity of the I-FOBT were calculated in correlation to age, size, and pathologic result.

Results: A total of 6096 patients were analyzed, including 3418 men and 2678 women, aged 40—87 years. I-FOBT result was positive in 229 patients (3.8%); the sensitivity of detection of total colorectal neoplasia and advanced neoplasia were 6.98% and 22.1%, respectively. A total of 13 participants were found to have invasive cancer in this study, and the sensitivity and specificity of the I-FOBT in this group were 69.2% and 96.4%, respectively. Besides, the positive rate of I-FOBT

* Corresponding author. Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Number 5, Fu-Sing Street, Gueishan Township, Taoyuan County 333, Taiwan.
E-mail address: hsu3060e@adm.cgmh.org.tw (C.-M. Hsu).

http://dx.doi.org/10.1016/j.aidm.2013.09.003

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Introduction

Colorectal cancer is a major public health issue due to its increasing prevalence and mortality in developed countries, and also in Taiwan. According to the statistics of the Department of Health (Taiwan), the age-standardized incidence of colorectal cancer has progressively risen over the past 20 years, from 1990 (17.10 per 100,000 in men and 14.73 per 100,000 in women) to 2009 (48.65 per 100,000 in men and 34.48 per 100,000 in women). Most cases of colorectal cancer are found sporadically, and the morbidity and mortality can be reduced with improvement in the early detection of precancerous lesions or of early-stage cancer. Therefore, a fecal occult blood test (FOBT) for colorectal cancer and advanced colonic polyps. As this test is not specific for human hemoglobin, some foods or medications may induce false-positive or false-negative results [2,3]. Diet restrictions are, therefore, needed prior to conducting a G-FOBT. Several studies have suggested that the immunochemical fecal occult blood test (I-FOBT) has better sensitivity than the conventional G-FOBT [4–6]. The I-FOBT makes use of antibodies specific to human hemoglobin, eliminating the necessity for dietary restrictions. In this study, we analyzed the sensitivity of a one-time, qualitative, I-FOBT for detecting colorectal neoplasia in asymptomatic population of different age groups.

Materials and methods

The study was designed to analyze retrospectively an asymptomatic population that underwent a health examination at the Health Care Center of Chang Gung Memorial Hospital (Guieshan, Taiwan). A total of 8258 nonhospitalized persons were consecutively enrolled between January 2008 and June 2009, after having undergone a simultaneous one-time, qualitative I-FOBT and a colonoscopy examination. We excluded 1584 participants, younger than 40 years, due to a lower prevalence of colonic neoplasia in this age group, according to a previous study [7]. Furthermore, 578 patients were excluded due to incomplete or missing information, the presence of established colorectal cancer or inflammatory bowel disease, visible rectal bleeding, or menstruation during the time of stool sample collection. Therefore, 6096 participants were included in our analyses.

Fecal sampling

A one-time I-FOBT was performed for each participant. The participants received an explanation and instructions for preparing the fecal sample from a stool specimen, along with collection kits. They were asked to write their name and the date of collection on the tube. Stool specimens were self-collected, using a sampling probe (Eiken Chemical, Tokyo, Japan) by scraping different areas of the stool specimen’s surface. The probe was then firmly reinserted into the tube and sealed. The collection kit was brought to the clinic on the day of the colonoscopy. The kits were sent to the laboratory for testing within 24 hours. The sample was processed using the OC-LIGHT system (Eiken Chemical). The fecal sample was diluted with sodium azide-containing buffer to stabilize the hemoglobin and then reacted with the antibody on the test strip. A positive result was indicated by the presence of blue lines on the test strip, with a detection range from 10 μg/g to 100 mg/g of feces. The sensitivity was 50 ng Hb/mL of buffer or 10 μg/g of feces.

Colonoscopy

Each participant was provided with 2 L of polyethylene glycerol electrolyte solution (1-day standard program) or two doses (45 mL each) oral sodium phosphate solution (2-day standard program) for bowel preparation at home. They were also instructed to eat a low-fiber diet or a clear liquid diet for 3 days prior to the colonoscopy. Incomplete studies or individuals improperly prepared were excluded from the study. Experienced endoscopists performed the colonoscopy and were blinded to the results of the I-FOBTs. All the neoplasms identified by colonoscopy were recorded by the endoscopists, but the largest or most advanced lesion was recorded in this study. Polyps <0.5 cm were removed using cold biopsy forceps. However, if a larger lesion (≥0.5 cm) was found, removal was performed by polypectomy or endoscopic mucosal resection. If invasive cancer was suspected, biopsy would be done for tissue proof first before further management. Patients who underwent a biopsy, polypectomy, or endoscopic mucosal resection were referred to the outpatient department for further management.
Pathological findings

Each specimen collected for biopsy or polypectomy was fixed in formaldehyde and sent for a pathological assessment. The pathologists were also blinded to the results of the I-FOBT. Histological characteristics of the polyps were recorded as the absence of neoplasia (including hyperplastic polyps), tubular adenoma (TA) <10 mm, TA ≥ 10 mm, adenoma with a villous component, high-grade dysplasia, or invasive cancer. Advanced neoplasia was defined as TA ≥ 10 mm, adenoma with a villous component, high-grade dysplasia, or invasive cancer.

Statistical analysis

We calculated the sensitivity and specificity of the I-FOBTs for detecting colorectal neoplasia, advanced neoplasia, and invasive cancer, on the basis of endoscopic and pathological findings of colonoscopy. In different age groups, the sensitivity, specificity, positive predictive values, and negative predictive values were also calculated. SPSS Statistics software version 17.0 (IBM Inc., Armonk, NY, USA) was applied for statistical analyses.

Results

Of the 8258 participants who enrolled, 2162 were excluded, leaving a total of 6096 adults (3418 men and 2678 women) for the analyses. The mean age of the patients was 53.65 ± 8.42 years (range, 40–87.0 years). Different age groups of participants were classified and analyzed, including those aged 40–49 years (2214 participants, 36.3%), 50–75 years (3794 participants, 62.2%), and >75 years (88 participants, 1.5%). No serious colonoscopy complications were recorded. The I-FOBT was positive in 229 participants (3.8%) and negative in 5867 (96.2%). Table 1 shows the basic characteristics of all the eligible participants; no significant differences were observed for each characteristic. As per the results of colonoscopy, no evidence of neoplasia was found in 4620 participants (75.8%), and TAs (<10 mm) were found in 1222 patients (24.2%). Advanced neoplasia was found in 254 patients, including TA (≥10 mm) in 80 patients (3.1%), adenoma with a villous component in 145 patients (2.4%), high-grade dysplasia in 16 patients (0.3%), and invasive cancer in 13 patients (0.2%). The size of the colonic neoplasia was also recorded, according to the results of colonoscopy and pathological findings.

In Table 2, characteristics of the colonic neoplasms and the diagnostic performance of the I-FOBTs are shown. Positive I-FOBTs were found in 47 (out of 1222) patients with TAs (<10 mm), with a sensitivity of 3.85%. However, the sensitivity of the I-FOBT in the group with advanced neoplasia increased to 22.1%, and up to 69.2% when invasive cancer was detected. However, four cases of invasive cancer were not detected by the I-FOBT. The overall sensitivity for detecting colorectal neoplasia was 6.98%. By contrast, out of 229 patients with positive I-FOBT results, neoplastic lesions were found in 103 patients (45.0%) and advanced neoplasia was found in 56 patients (24.5%). In I-FOBT-negative patients, 23.4% demonstrated neoplasia (1373 of 5867), with only 3.4% having advanced neoplasia (198 of 5867). An increased risk of neoplasia was found in the group with positive I-FOBT results compared to the group with negative I-FOBT results, with a relative risk of 1.92. The same result was also found in the group with advanced neoplasia, in patients with positive I-FOBT results; the relative risk was 7.25 compared with patients with negative I-FOBT results. For colorectal neoplasia and advanced neoplasia, the rates of false-positive results were 2.73% and 2.96%, and that of false-negative results were 93.0% and 78.0%, respectively. The positive and negative predictive values of total colorectal neoplasia (45.0%, 76.6%) and advanced neoplasia (24.5%, 96.6%) were also analyzed.

Table 3 shows the I-FOBT results and colonoscopy findings in patients stratified by age categories. The percentage of advanced neoplasia among all colorectal neoplasia increased with age: 14.7% (56/380) in those aged 40–49 years, 18.0% (192/1069) among 50–75-year olds, and 22.2% (6/27) in individuals aged >75 years. The positive rate, sensitivity for total neoplasia, and positive predictive value of I-FOBT also increased with age. Increased I-FOBT
sensitivity for advanced neoplasia, compared with total neoplasia, was also found in each age group. Invasive cancer was detected in the age groups of 40–49 years and 50–75 years, with a total of 13 patients found to have invasive disease. In the subdivided groups of patients ≥40 years of age, the sensitivity for detecting advanced neoplasia (22.0%) and the positive predictive values (24.5%) were similar to those of the subdivided groups of age ≥50 years (19.2% and 23.0%, respectively).

### Discussion

Recent treatment guidelines have recommended that annual I-FOBTs replace annual G-FOBTs for colorectal cancer screening [8]. This examination for cancer screening is easy and feasible, and several studies have shown that its sensitivity for colorectal neoplasm ranges from 56% to 91% and specificity from 88.2% to 97% [7,9–13]. Other studies have also compared the I-FOBT with colonoscopy in the general population [7,14]. Previous studies reported that the I-FOBT has improved sensitivity for detecting colorectal cancer and advanced adenomatous polyps compared to guaiac-based occult blood test [9,15–19]. In addition, the I-FOBT is less affected by food, eliminating the need for dietary restrictions prior to the test. In Taiwan, the FOBT has been advocated by the Bureau of Health Promotion for individuals over 50 years of age. Here, we examined the prevalence of colorectal neoplasia and the detection of advanced colonic neoplasia by using the I-FOBT, among patients in different age groups, which may affect clinical decision making and screening strategies.

In this study, a qualitative I-FOBT, based on immuno chromatographic technology, was used to evaluate stool occult blood, with a sensitivity of 50 ng Hb/mL. A similar study evaluated the qualitative FOBT method in 5841 participants [20]. However, that study evaluated only distal colonic lesions by sigmoidoscopy rather than by colonoscopy. The sensitivity for distal advanced neoplasms was 33.1%. Our study revealed that the sensitivity of the one-

### Table 2  Diagnostic performance of I-FOBT and correlation of colonoscopy results.

<table>
<thead>
<tr>
<th>Colonoscopy findings</th>
<th>I-FOBT</th>
<th>Total (%)</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoplasia</td>
<td>4944 (76.6)</td>
<td>126 (55.0)</td>
<td>4620 (75.8)</td>
<td></td>
</tr>
<tr>
<td>Total neoplasia</td>
<td>1373 (23.4)</td>
<td>103 (45.0)</td>
<td>1476 (24.2)</td>
<td>6.98 (5.68–8.28) 97.3 (96.8–97.7)</td>
</tr>
<tr>
<td>Tubular adenoma &lt;10 mm</td>
<td>1175 (20.0)</td>
<td>47 (20.5)</td>
<td>1222 (20.0)</td>
<td>3.85 (2.77–4.92) 96.3 (95.7–96.8)</td>
</tr>
<tr>
<td>Advanced neoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular adenoma ≥10 mm</td>
<td>69 (1.2)</td>
<td>11 (4.8)</td>
<td>80 (1.3)</td>
<td>13.8 (6.2–21.3) 96.4 (95.9–96.9)</td>
</tr>
<tr>
<td>Adenoma with villous component</td>
<td>114 (1.9)</td>
<td>31 (13.5)</td>
<td>145 (2.4)</td>
<td>21.4 (14.7–28.1) 96.7 (96.2–97.1)</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>11 (0.2)</td>
<td>5 (2.2)</td>
<td>16 (0.3)</td>
<td>31.3 (8.54–54.0) 96.3 (95.8–96.8)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>4 (0.1)</td>
<td>9 (3.9)</td>
<td>13 (0.2)</td>
<td>69.2 (44.1–94.3) 96.4 (95.9–96.9)</td>
</tr>
<tr>
<td>Total</td>
<td>198 (3.4)</td>
<td>56 (24.5)</td>
<td>254 (4.2)</td>
<td>22.1 (17.0–27.2) 97.0 (96.6–97.5)</td>
</tr>
<tr>
<td>Total</td>
<td>5867</td>
<td>229</td>
<td>6096</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; I-FOBT = immunochemical fecal occult blood test.

### Table 3  Results of colonoscopy and I-FOBT in different age groups.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No neoplasia</th>
<th>Tubular adenoma &lt;10 mm</th>
<th>Advanced neoplasia</th>
<th>Total</th>
<th>I-FOBT positive rate (%)</th>
<th>Sensitivity of total neoplasia (%) (95% CI)</th>
<th>Sensitivity of advanced neoplasia (%) (95% CI)</th>
<th>Positive predictive value for advanced neoplasia (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 y</td>
<td>39/1834</td>
<td>7/324</td>
<td>5/17</td>
<td>41/2214</td>
<td>2.89</td>
<td>6.58 (4.1–9.1)</td>
<td>32.1 (19.9–44.4)</td>
<td>28.1 (17.1–39.1)</td>
</tr>
<tr>
<td>50–75 y</td>
<td>85/2725</td>
<td>39/877</td>
<td>6/61</td>
<td>160/3794</td>
<td>4.21</td>
<td>7.02 (5.48–8.55)</td>
<td>18.8 (13.2–24.3)</td>
<td>22.5 (16.0–29.0)</td>
</tr>
<tr>
<td>&gt;75 y</td>
<td>2/61</td>
<td>1/21</td>
<td>0/2</td>
<td>5/88</td>
<td>5.68</td>
<td>11.1 (0–23.0)</td>
<td>33.3 (0–71.1)</td>
<td>40.0 (0–82.9)</td>
</tr>
<tr>
<td>≥50 y</td>
<td>87/2786</td>
<td>40/898</td>
<td>6/63</td>
<td>165/3882</td>
<td>4.25</td>
<td>7.12 (5.59–8.64)</td>
<td>19.2 (13.7–24.7)</td>
<td>23.0 (16.6–29.5)</td>
</tr>
<tr>
<td>≥40 y</td>
<td>126/4620</td>
<td>47/1222</td>
<td>6/63</td>
<td>229/6096</td>
<td>3.76</td>
<td>6.98 (5.68–8.28)</td>
<td>22.0 (17.0–27.2)</td>
<td>24.5 (18.9–30.0)</td>
</tr>
</tbody>
</table>

CI = confidence interval; I-FOBT = immunochemical fecal occult blood test.
time I-FOBT was 6.98% for total colorectal neoplasia and 22.1% for advanced neoplasia; the specificities were 97.3% and 97.0%, respectively. The sensitivity for the detection of invasive cancer was 69.2%, with 96.4% specificity. Although the sensitivity and specificity of FOBT may be affected by the cut-off values used, our results were similar to those found in a previous, large-scale study involving 21,805 asymptomatic adults where a quantitative FOBT was used [7].

The sensitivity of the I-FOBT was 6.98% (103/1476) for total colorectal neoplasia, 22.1% (56/254) for advanced neoplasia, and 69.2% (9/13) for invasive cancer, with increasing sensitivity being associated with advanced pathological grades, which may be helpful for cancer screening. Similar results were also found in previous studies [7,14]. Early detection of advanced neoplasia is important for the early management of colorectal neoplasms. Hofstad et al. [21] found that one-fourth of the patients with adenomas <10 mm have a tendency for net growth, and patients with multiple adenomas have more new polyps than those with a single adenoma. Clark et al. [22] also reported the results from an autopsy series that showed that only 2.5/1000 polyps per year progress to cancer, and Ransohoff [23] stated that large adenomas progress to cancer at a rate of approximately 1% per year. Other studies have also shown that annual or biennial FOBTs [24,25] can reduce the mortality of colorectal cancer. Therefore, although the sensitivity of the I-FOBT was low in this study, repeated I-FOBTs may be beneficial for cancer screening and early management, to avoid the progression of colonic neoplasia.

Moreover, we found that the proportion of advanced neoplasms may be associated with age, as shown in Table 3. Since health examination is increasingly universal in Taiwan, and also increasing number of middle-aged people paid attention and joined the examinations, so we subdivided our study population into three age groups (40–49, 50–75 and ≥75) and tried to analyze the differences between age categories. The positive rate of the I-FOBT and its sensitivity for total neoplasia were found to have similar correlations to age. Most colon cancers are generally accepted to have originated from previous adenomas. The prevalence rates for both adenomatous polyps and cancer increase with age, and previous studies have shown that, as age distribution curves have revealed, adenomas may be followed by carcinomas within 5–10 years [26,27]. Therefore, an early detection of colorectal malignancy or advanced neoplasia has been emphasized. Our participants were also stratified into two age categories, those ≥50 years and those ≥40 years, for additional analyses in order to assess the effect of starting screening 10 years earlier than the age recommended by the Bureau of Health Promotion in Taiwan. The sensitivity of detection of total neoplasia in these 2 groups did not differ significantly (≥50 years: 7.12%, ≥40 years: 6.98%), as did the detection of advanced neoplasia in these 2 age groups (≥50 years: 19.2%, ≥40 years: 22.0%). The American College of Gastroenterology-recommended age for starting colorectal cancer annual screening is also 50 years among individuals with an average risk and 45 years for African Americans [8]. Furthermore, the literature supports the notion that cigarette smoking and obesity are associated with an increased risk of colorectal cancer at an earlier age, which is also mentioned in the American College of Gastroenterology guidelines [8]. Therefore, earlier screening, beginning at an age of 40 years, with the I-FOBT may be considered, at least in members of the population at higher risk, such as those who are heavy smokers, obese, or have a familial history of colon cancer or related neoplasia. Further study is needed to determine the age and the population at increased risk for beginning I-FOBT.

Our study had several limitations. First, small polyps may be missed due to the accuracy limits of colonoscopy, even when performed by an experienced endoscopist. This may result in an underestimation of the prevalence of colonic neoplasia. Second, this was a retrospective study and selection bias may be a defect of the population under study. Besides, the sensitivity and positive predictive values decreased in the age group of 50–75 years, which may be affected by the heterogeneous study population with mixture of different risk groups, including first-time screening or received prior surveillance of colorectal neoplasms. Third, first-screening and surveillance patients could not be distinguished due to a lack of clinical information, which may restrict the external validity and applicability of the study results to the general population. Fourth, the 1-day method of I-FOBT may reduce the sensitivity for the detection of small adenomatous polyps or other advanced neoplasia. However, the use of the 2- or 3-day method may probably increase both the sensitivity and the rate of false positives, as well as minimize the compliance of the participants involved in the health examination. Therefore, a single examination of the I-FOBT could not exclude negative screening of colorectal neoplasia. By contrast, different cut-off values of the I-FOBT may also affect the screening result. No consensus or randomized study has been made that the adequate cut-off value of I-FOBT, except one large-scale study in 2007 with assessment of the cost-effectiveness of I-FOBT and identified 110 ng/mL as the optimal cut-off [28]. Lastly, we did not possess other clinical information for further evaluation of the participants, such as family history, dietary habits, etc. These types of data would have provided additional information for evaluation and helped avoid selection bias.

In conclusion, we demonstrated the sensitivity of a one-time I-FOBT for detecting advanced colonic neoplasia in a retrospective study involving asymptomatic individuals from Taiwan. Although the sensitivity was relatively low, similar to those in previous studies, repeated studies may be beneficial for the early management of advanced colonic neoplasia and colorectal cancer, helping to minimize morbidity and mortality. Besides, receiving the I-FOBT at an earlier age (40 years) may also be beneficial for the early detection of advanced colorectal neoplasms. Our study may promote further research on the I-FOBT and early detection of colonic neoplasia, including assessment of the cost-effectiveness of I-FOBT for different age categories and risk groups in Taiwan, and may clarify the unresolved issues and improve our national health policy.

Conflicts of interest
All authors declare no conflicts of interest.
References


