The effectiveness of screening tests for colorectal cancer on employees: the usefulness of annual check-ups.

Ryuichi KURIHARA, Ariyoshi IWASAKI, Yasuyuki ARAKAWA

The Third Department of Internal Medicine, Nihon University School of Medicine

Summary

Screening surveillance for colorectal cancer using immunological fecal occult blood tests has been actively conducted to achieve early detection and treatment. In our facilities, we have conducted screening tests for colorectal cancer on employees since 1988. In this study, we examined the cases of colorectal cancer and adenoma detected by the screening, and compared the one-day method with the two-day method, barium enema examination with colonoscopic study in diagnostic effectiveness, and assessed the usefulness of annual screening tests. 1) Immunological fecal occult blood tests; the detection rate of the one-day and two-day method were both 0.14%, yielding no difference. 2) The agreement rate of the results between barium enema and colonoscopic examination was low in the proximal colon. 3) The more annual screening tests each individual underwent, the less frequently colorectal cancer was detected. At the fourth time or later, no advanced cancer was detected. Furthermore, no colorectal cancer including early cancer was detected in the individuals who underwent six consecutive screening tests. Taken together, annual screening tests were useful, but further reviewing is warranted to employ barium enema examination as the first scrutinizing test.

Key words
1. screening tests for colorectal cancer on employees.
2. annual check-ups
3. immunological fecal occult blood test

Introduction

Recently the number of detected colorectal cancer has been increasing every year in part due to the Westernized eating habits. More than 20 years have passed since the introduction of mass screening tests for gastric cancer in Japan, which has facilitated early detection and contributed to the decreased mortality by the following surgery at early stages. Fecal occult blood tests were developed to efficiently detect colorectal cancer, aiming to decrease mortality rates by finding and treating it at early stages. These screening tests have been employed in more and more facilities. In the facilities associated with our department, screening tests for colorectal cancer on employees have been conducted, and the following items were examined in this study. 1) Fecal occult blood tests: comparing the one-day and the two-day method. 2) Comparison of barium enema and colonoscopic examination in terms of diagnostic effectiveness. 3) The usefulness of annual screening tests.
Table 1 : Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>91 cases (279 tumors) treated by endoscopic polypectomy were analyzed</td>
<td>Barium enema examination</td>
</tr>
<tr>
<td></td>
<td>SCG method</td>
</tr>
<tr>
<td></td>
<td>Colonoscopic examination</td>
</tr>
<tr>
<td></td>
<td>Endoscopic observation and treatment were carried out separately, and each case was examined endoscopically at least twice</td>
</tr>
<tr>
<td>Agreement rate =</td>
<td>( \frac{\text{Barium enema}}{\text{Colonoscopy}} \times 100 )</td>
</tr>
</tbody>
</table>

Figure 1 : Subjects

Subjects and Methods

1) Fecal occult blood tests.

The one-day method was conducted for 32,449 individuals who visited the facilities affiliated with our department from fiscal 1988 through 1991, and the two-day method was employed for 25,776 in fiscal 1992 and 1993.

2) Diagnostic effectiveness of barium enema and colonoscopic examination.

Ninety-one cases (279 tumors) treated by endoscopic polypectomy at Surugadai Nihon University Hospital were analyzed. These cases were diagnosed as colorectal polyps by barium enema examination in the facilities associated with our department, and referred to Surugadai Nihon University Hospital for the indication of endoscopic polypectomy. Endoscopic examination and intervention such as endoscopic polypectomy and mucosal resection were performed and each case was examined at least twice endoscopically. In cases polyps were found by the examinations, the agreement rates were calculated as follows:

Agreement rate = the number of polyps detected by barium enema examination / the number of polyps found by colonoscopic examination X 100 (Table 1).

3) Annual screening tests.

A total of 29,254 examinees in the facilities affiliated with our department and eight companies which had a contract for screening tests with our department were analyzed. They were 46.7 years old on average, and a male-to-female ratio was 7:1. The age distribution of the examinees is shown in Figure 1. Compared with the screening tests based on the regions, the screening tests on employees had fewer elderly people aged 60 or older. The flowchart of examinations is demonstrated in Figure 2. The primary screening adopted the RPHA method, an immunological fecal occult blood test. (the
Table 2: Comparison of 1-day and 2-day method fecal occult blood tests

<table>
<thead>
<tr>
<th></th>
<th>1988 to 1991 (1-day method)</th>
<th>1992 to 1993 (2-day method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of subject</td>
<td>32,449</td>
<td>25,776</td>
</tr>
<tr>
<td>Numbers of positive</td>
<td>1,381</td>
<td>1,590</td>
</tr>
<tr>
<td>Percentage of positive</td>
<td>4.3%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Adenoma</td>
<td>212 (0.65%)</td>
<td>204 (0.79%)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>44 (0.14%)</td>
<td>37 (0.14%)</td>
</tr>
</tbody>
</table>

Figure 3: Comparison of the detection rates for colorectal adenoma and cancer

Figure 4: Agreement rates for colorectal adenoma

Results
1) Comparison of the one-day and two-day method of a fecal occult blood test.

As shown in Table 2, the one-day method was employed from fiscal 1988 through 1991. Out of 32,449 examinees, 1,381 tested positive accounting for 4.3%. On the other hand, the two-day method was carried out in 1992 and 1993, and 1,590 tested positive accounting for 6.2% of the total examinees of 25,776. As shown in Figure 3, the detection rate for colorectal cancer was 0.14% in both the one-day and the two-day method, yielding no difference. The sensitivity for colorectal adenoma was 0.65% by the one-day method, while it was higher and 0.79% by the two-day method.

2) Agreement rates in the results between barium enema and colonoscopic examination.

As shown in Figure 4, the agreement rate of detecting colorectal adenoma was over 80% in the location of the rectum and the sigmoid colon, whereas it was as low as 25% and 30% in the ascending colon and the cecum, respectively. As shown in Figure 5, when the analysis was limited to the adenomas equal to or larger than 5 mm in size, the agreement rate was highest (95%) in the descending colon followed by 91% in the transverse colon and 89% in the rectum, while it was as
low as 20% in the ascending colon.

Agreement rates by macroscopic morphological classification were analyzed. As shown in Figure 6, the morphological agreement rate was 82.6% for Is, 75% for Isp, and 77% for Ip, resulting in the highest in Is. The agreement rate in terms of location was high in the rectum and the sigmoid colon, while it was low in the ascending colon, with no association of the location of the tumor and the macroscopic morphology.

Figure 7 demonstrates the agreement rates for early colorectal cancer. No early cancer was detected in the proximal colon in this study. The agreement rate was 100% both in the rectum and the sigmoid colon, and 50% in the descending colon. The case with discrepancy in the descending colon was Ip with 10mm in diameter.

3) Annual screening.

Table 3 shows the positive test rates in relation to the number of screening tests taken. The number of those who underwent screening tests six consecutive times was 1,423. The positive rate stayed on the four percent level for the first-time through third-time examinees, while it was 5.3% for the fourth-time subjects, and 6.3% and 6.5% for the fifth- and the sixth-time examinees.
Table 4: Abnormalities and the numbers of examinations

<table>
<thead>
<tr>
<th></th>
<th>1st time</th>
<th>2nd time</th>
<th>3rd time</th>
<th>4th time</th>
<th>5th time</th>
<th>6th time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>190</td>
<td>126</td>
<td>109</td>
<td>104</td>
<td>83</td>
<td>58</td>
</tr>
<tr>
<td>Diverticulum</td>
<td>37</td>
<td>27</td>
<td>28</td>
<td>30</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Adenoma</td>
<td>51 (0.57)</td>
<td>48 (0.71)</td>
<td>38 (0.73)</td>
<td>30 (0.73)</td>
<td>25 (0.83)</td>
<td>10 (0.70)</td>
</tr>
<tr>
<td>Cancer</td>
<td>25 (0.29)</td>
<td>8 (0.13)</td>
<td>4 (0.08)</td>
<td>4 (0.10)</td>
<td>3 (0.10)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Colitis</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>305</td>
<td>209</td>
<td>180</td>
<td>168</td>
<td>135</td>
<td>77</td>
</tr>
<tr>
<td>Numbers of subjects</td>
<td>8961</td>
<td>6749</td>
<td>5195</td>
<td>4119</td>
<td>3007</td>
<td>1423</td>
</tr>
</tbody>
</table>

Table 5: The number of annual screening tests and colonic adenoma

<table>
<thead>
<tr>
<th></th>
<th>1st time</th>
<th>2nd time</th>
<th>3rd time</th>
<th>4th time</th>
<th>5th time</th>
<th>6th time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>28</td>
<td>28</td>
<td>21</td>
<td>17</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Multiple</td>
<td>23</td>
<td>20</td>
<td>16</td>
<td>13</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 10 mm</td>
<td>32</td>
<td>37</td>
<td>27</td>
<td>27</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Above 10 mm</td>
<td>19</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>48</td>
<td>30</td>
<td>25</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8: Detection rates in relation to the number of examinations for cancer and colonic adenoma

Table 6: Numbers of examinations and detected colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>1st time</th>
<th>2nd time</th>
<th>3rd time</th>
<th>4th time</th>
<th>5th time</th>
<th>6th time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early cancer</td>
<td>18</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

respectively. The rates of taking thorough examination were around 80% regardless of the number of the past examinations; in other words, they did not change remarkably in spite of the repeated examinations.

Table 4 shows the relationship between the number of the past examinations and the detected abnormalities, and Figure 8 demonstrates changes of the detection rates for colorectal cancer and adenoma in relation to the number of the past examinations. The three cases found in the first- and third-time examinations revealed colitis. Colorectal adenoma was found in 51 cases (detection rate, 0.57%) by the first, 48 (0.73%) by the second, 38 (0.73%) by the third, 30 (0.73%) by the fourth, 25 (0.83%) by the fifth, and 10 (0.70%) by the sixth examination, and the number of the past examinations had no correlation with the detection rates.

Table 5 shows the adenomas found in relation to the history of annual examinations. Regardless of the numbers of annual screening tests taken, the incidences of solitary and multiple adenomas did not differ remarkably. On the other hand, the percentage of large adenomas equal to or larger than 10mm in diameter accounted for 37% in the first-time scrutiny, and decreased in relation to the numbers of examinations. For persons who had undergone more than four checkups, the percentage of adenomas above 10 mm in size was below 10%.

Table 6 shows numbers of examinations and detected colorectal cancer. Twenty-five subjects were detected with cancer (early stage: 18 subjects, advanced stage: 7 subjects) amongst persons.
receiving checkups for the first time, eight subjects (early stage: 4 subjects, advanced stage: 4 subjects) amongst persons receiving checkups for the second time, four subjects (early stage: 2 subjects, advanced stage: 2 subjects) amongst persons receiving checkups for the third time, four subjects (early stage: 4 subjects) amongst persons receiving checkups for the fourth time, three subjects (early stage: 3 subjects) amongst persons receiving checkups for the fifth time, 0 amongst persons receiving checkups for the sixth time. The number of colorectal cancers discovered decreased as the number of checkups increased, and no advanced cancers were discovered after the fourth checkup. Furthermore, not one case of cancer was discovered in persons undergoing six annual checkups consecutively.

Figure 9 demonstrates the morphological classification and the location of colorectal cancer found in the examinations taken more than once. Four cases of early cancer (Is, 2; and Ip, 2) and four advanced cases were observed by the second examination. Two early (Ip) and 2 advanced cancers, and 4 early (IIa + IIC, 1; Is, 1; and Ip, 2) and no advanced cancers were observed by the third and the fourth examination, respectively. Three cases of early cancer was found by the fifth examination, two of which were synchronous double cancers (Is, 3; Isp, 1; and Ip, 2). There was a tendency that cancer was found in the further proximal colon as the number of examinations increased.

**Discussion**

1) Fecal occult blood tests: comparing the one-day and the-two day method.

We employed the RPHA method, one of fecal occult blood tests, in our facilities. The one-day method screened 32,449 individuals from fiscal 1998 through 1991, with positive tests in 1381 (4.3%). The two-day method screened 25,776 subjects in 1992 and 1993, with 6.2% suggested for further examination. The detection rate of colorectal cancer was 0.14% by both the one-day and the two-day method, resulting in no difference between the two methods. The detection rates of colorectal adenoma were 0.65% by the one-day method and 0.79% by the two-day method.

Lately immunological fecal occult blood tests including the RPHA method are mainly employed for screening colorectal cancer. However, 20 kinds of immunological occult blood test kits are commercially available now. Soma et al. addressed the necessity to examine and choose the most suitable kit for each facility because there had been few reports comparing the usefulness of these kits objectively, and their methods of collecting stool samples, reaction time, judgment timing, and conveniences are different.

Iwase et al. investigated the detection rates of early cancer depending on the number of collected stool samples, and reported that the one-day method did not overlook advanced cancer and picked out about half of early cancers. Moreover, 75% of early cancer was detected by the three-day
method. Considering the efficiency, sensitivity, specificity, and compliances, they reported that the one-day or the two-day method for collecting stool samples would be appropriate. Miyoshi et al.\textsuperscript{3} reported that the three-day method was desirable because of the high detection rate. Arai et al.\textsuperscript{4} reported a more efficient way of screening colorectal cancer using questionnaire. Yoshida et al.\textsuperscript{5} mentioned that examining the relationship between the number of days to collect stool samples and the estimated detection of colorectal cancer, the one-day method provided a better detection rate but overlooked 17.8\% of cancer, 30\% of early cancer and 10\% of advanced cancer, which would be detected by the two-day method, and the decrease of a detection rate by 20\% was not acceptable even though mass screening needed to strike a balance between the efficiency and the effectiveness. Therefore, the two-day or the three-day method using an immunological fecal occult blood test is recommended for screening colorectal cancer. However, there was no difference in detecting cancer between the one-day and the two-day method in our facilities, and consecutive annual examinations made it possible to efficiently detect colorectal cancer by the one-day method and decrease the mortality, satisfying the original objective of cancer screening tests.

2) Comparison of barium enema and colonoscopic examination in terms of effectiveness.

In this study, the agreement rate was analyzed comparing the results of barium enema and colonoscopic examination. The agreement rate on total colorectal adenomas was about 62\% and high in the rectum and the sigmoid colon, whereas low in the ascending colon and the cecum.

The potential reason of the low agreement rates in the proximal colon was that insufficient preparation for barium enema examination made it difficult to detect lesions in the proximal colon especially for constipation-prone examinees, and inflating the proximal colon with air was more difficult in examinees with multiple diverticula in the proximal colon, resulting in obtaining poor double-contrast images. In addition, technically insufficient delivery of barium into the proximal colon made it difficult to obtain good images.

On the other hand, although the low agreement rate in the rectum and the sigmoid colon was often argued, it was not observed in this study. This may be ascribed to the efforts to avoid the overlapping images of bowels enough to provide sufficient information for diagnosis.

There was no early cancer in the proximal colon, and the total agreement rate for early cancer was 95\%. The only one case with discrepancy was Ip in the descending colon. This may indicate that barium enema examination is appropriate for the first scrutiny.

Fuchigami et al.\textsuperscript{6} examined the most appropriate modality for mass screening of colorectal cancer. They compared three modalities, barium enema examination, total colonoscopic examination, and a combination of flexible sigmoidoscopy and barium enema examination, finding no remarkable difference in the effectiveness of detecting colorectal cancer, which was similar to our results. However, Mitsushima et al.\textsuperscript{7} pointed out the low agreement rate of barium enema and colonoscopic examination (especially, 21\% for colorectal adenoma), and total colonoscopy should be chosen as the scrutinizing modality.

Given the situation that there are rapidly increasing examinees of mass screening tests for colorectal cancer and shortage of facilities and colonoscopists for scrutiny, the best way may be to...
choose the modality to scrutinize total colon thoroughly depending on the situation of the facilities.

3) The usefulness of annual check-ups.

As to colorectal adenomas found by the annual check-ups, neither solitary or multiple lesions depended on the number of past annual check-ups. However, the percentage of adenomas 10mm or larger in size decreased in relation to the number, and adenomas 10mm or larger in size found in the fourth examination or later accounted for equal to or less than 10%. Otaki et al reported that most of adenomas equal to or larger than 10mm in size could be detected by the two-day method even if they were solitary. In addition, multiple adenomas, even if equal to or less than 9mm in size, would reveal positive by fecal occult blood tests. Our results indicated that not all of the adenomas bled but adenomas equal to or larger than 10mm bled at a certain rate to be detected by fecal occult blood tests. On the other hand, adenomas equal to or less than 10mm in size, even if multiple, could not be detected. Accordingly, even if adenomas equal to or less than 10mm in size, usually difficult for detection, failed to be found by the screening, annual check-ups would provide several times of opportunities to detect them. As to colorectal cancer, 25 cases (detection rate, 0.29%), 8 (0.13%), 4 (0.08%), 4 (0.10%), and 3 (0.10%) were detected by the first through the fifth examination, respectively. The more annual check-ups they took, the less frequently new lesions were found, and no cancer was detected in the sixth-time examinees.

The total detection rate of colorectal cancer was 0.15% in this study. Kawamura et al reported that the detection rate by the two-day method using OC-Hemodia (Eiken Chemical Co. Ltd., Tokyo, Japan) was 0.26%, while Shimada et al at the Miyagi Cancer Association reported 0.27% by the two-day method using the RPHA method. Therefore, the rate in our facilities revealed lower in the current study. Different age distribution in our study, a remarkably small population of the aged 60 years old or older because of the regions and occupations, may explain this result. Other potential reasons are differences in the way of collecting stool samples and the modalities for the scrutiny. The modality for thorough examination recommended by JSGMS is either sigmoidoscopy followed by barium enema examination or total colonoscopy. Mitsushima et al reported that no advanced cancer was overlooked by a combination of barium enema and colonoscopic examination, but 35% and 15% of polypoid lesions (5mm or larger) were not detected by barium enema and colonoscopic examination, respectively. Thus, ideally speaking, total colonoscopy should be chosen as the first modality for scrutiny. Taking into consideration the situation that there are not sufficient facilities or staff to examine the increasing subjects, screening colonography (SCG) employed in our facility for the first scrutiny with total colonoscopy for the second thorough examination may be appropriate based on the premise of annual check-ups.

Next we further examined the usefulness of annual check-ups for colorectal cancer. There were 25 cases of colorectal cancer found by the first-time screening test, while 19 cases were found by the successive annual check-ups, accounting for 43%. Narumoto et al reported that 33% of colorectal cancer was found by the successive annual check-ups, and about 30% of colorectal cancer found by the annual check-ups was pointed out by the successive check-ups. They, therefore, emphasized the importance of annual check-ups.
Early colorectal cancer accounted for 4 of 8 cancers found by the second annual check-up, 1 of 3 by the third check-up, while 4 and 3 early cancers, without any advanced cancer, were found by the fourth and the fifth check-up, respectively, and they were cured by endoscopic treatment, indicating the importance of annual check-ups. Narumoto et al.12) likewise analyzed the relationship of the advancement of cancer with the number of the past annual check-ups, and reported that the first-time check-up and the consecutive check-ups made it possible to detect 65% and 70% of early cancers, and 85% and 90% of Dukes A cancers in all advanced cancers, respectively. It was notable that both numbers were higher by the consecutive check-ups, which corresponded to our results. Nakama et al.13,14) reported that during the seven years of consecutive annual check-ups 16 colorectal cancers, comprising 12 early and 4 advanced cases, were detected, and the early cases accounted for as high as 75% and all the colorectal cancers found at the fourth year or later were early cases, resulting in the survival rate of 93.8%. In addition, the standardized mortality rates (SMRs) of colorectal cancer before and after the implementation of annual check-ups were 108.7 and 50.1, respectively, and an early effect as well as a late effect was recognized. This report also showed that all cancers detected at the fourth check-up or later were early cases, which notably corresponded to our results. Collectively, the consecutive annual check-ups make it possible to not only detect colorectal cancer overlooked by the first test but also find cancer at early stages, which enables less invasive endoscopic treatment and subsequently lowers the mortality by colorectal cancer, achieving the final goal of mass screening tests.

Problems with consecutive annual check-ups lie in the difficulties to have the subjects undergo testing every year and the occurrence of cancer between the check-ups. In not only our facility but also others, the low rates of taking repeated tests were concerned. As a countermeasure, we need to enlighten subjects with the importance of annual check-ups and encourage them to take tests. Matsuda et al.15) examined the cancer which was found with symptoms leading to examination or appeared within one year in spite of the last negative fecal occult blood test for screening, and found that the false negative rate was 19.4%. In our affiliated facilities, there was no such case. In spite of a caveat that screening tests for colorectal cancer have been emphasized a little too much recently16), the number of subjects taking screening tests for colorectal cancer is still about half of that for gastric cancer in Japan. Therefore, we think that we have to keep on making efforts to promote annual check-ups for colorectal cancer.

**Conclusion**

We obtained the following results in screening tests for colorectal cancer in our facilities.

1) Immunological fecal occult blood tests: we compared the one-day method with the two-day method, finding no difference.

2) The agreement rate of the results between barium enema and colonoscopic examination was low for abnormalities in the proximal colon, indicating the problem with barium enema examination.

3) The more consecutive annual check-ups subjects took, the less frequently cancer was found, and there was no colorectal cancer detected by the sixth-time examinees.
Taken together, the importance of annual check-ups for colorectal cancer was corroborated. Barium enema examination as a modality for the first scrutiny needs to be reviewed for improvement.

The gist of this paper was presented in the symposium I in the general assembly of the 34th JSGMS meeting, "the limitations and future perspectives of mass screening tests for gastric and colorectal cancer" (May, 1995, Tokyo).

References
12) Narumoto H, Yano K, Matsuda S, et al. [Evaluation of sequential (every-year) mass screening for