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Diagnostic Validity of Fecal Occult Blood Tests for Detecting Gastroenterological Cancers

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In order to estimate the diagnostic validity of chemical fecal occult blood tests, i.e. orthotolidine (Shionogi A) and guajac (Shionogi B) slides for detecting cancers of the esophagus, stomach and colorectum, the authors followed up all the examinees (n=3,449) of comprehensive medical check-ups at the Center for Adult Diseases, Osaka, by means of record linkage to the Osaka Cancer Registry's files. Then, diagnostic validity was calculated based on the results of two years' follow-up. Sensitivity for the respective cancers was 20.0%, 11.8% and 62.5% for Shionogi A, and 20.0%, 5.9% and 43.8% for Shionogi B slides. Likelihood ratio for the respective cancers was 1.4, 0.8 and 4.5 for Shionogi A, and 3.3, 1.0 and 7.5 for Shionogi B. Specificity was analogous among the three cancer sites, being 86% for Shionogi A and 94% for Shionogi B. These results suggest that the diagnostic validity of chemical occult blood tests for detecting cancers of the esophagus and the stomach is very poor, and therefore imply that close examinations of these sites for screening positives is unnecessary in mass screenings for colorectal cancer.

Key words: Fecal occult blood test — Screening — Gastroenterological cancer — Diagnostic validity — Comprehensive medical check-up

In recent years the mortality from colorectal cancer has been increasing in Japan, and it is predicted that the mortality from this cancer will exceed that from gastric cancer, the present No. 1 killer cancer in Japan, by around the year 2000.[1)] Thus, in order to establish a secondary prevention program to cope with this rise in mortality, a number of mass screening programs for colorectal cancer, primarily screening by fecal occult blood tests (FOBT), are being tested in this country.[2)]

In mass screening programs for colorectal cancer by FOBT, screenees with positive results are supposed to undergo further work-up examinations of the colorectum such as a barium enema study or colonoscopic examination. Patients showing no significant findings from these examinations (false-positives) are not required to undergo further work-up examinations of the upper gastrointestinal tract in western countries, where the incidence of cancers of this site is very low.[3)] In Japan where the incidence of gastric cancer is very high, however, there has so far been no agreement on whether close examinations of the upper gastrointestinal tract should be recommended for such patients or not.

The aim of the present study was to estimate the diagnostic validity of FOBT for detecting cancers of both the lower and upper gastrointestinal tract and to solve the problem of how to deal with false-positives in these tests in colorectal cancer screenings in Japan.

In general, the validity of screening tests employed in mass screening programs is different from that estimated by testing retrospectively a group of patients hospitalized for, or otherwise known to have, the target disease. This is partly because the stage distribution tends to be considerably different between the two situations. Thus, to estimate the validity of mass screenings by FOBT for detecting gastroenterological cancers, it is very important to follow up all the screenees for a certain period and to identify all false-negative cases.[4, 5)]

In the present study, the authors followed up all the examinees of comprehensive medical check-ups, including chemical FOBT, by means of record linkage to the Osaka Cancer Registry files.

MATERIALS AND METHODS

At the hospital in our Center, the tests performed at the comprehensive medical check-ups included a medical questionnaire, physical examination, blood pressure measurement, chest X-ray, electrocardiogram, barium study for upper gastrointestinal tract, urinalysis, blood tests including hematology and serum chemistry panels, FOBT and so forth.

The kits used for FOBT were Shionogi A (orthotolidine) and Shionogi B (guajac) slides (Shionogi Pharmaceutics Co., Osaka). In general, the former is far more

sensitive for human blood detection than the latter. Feces after 3 days of dietary restriction were collected and smeared onto both slides simultaneously by clinical technicians without rehydration. The occult blood tests were immediately examined by the same technicians.

From 1981 through 1985, a total of 3,467 people (2,709 different individuals) whose residences were within Osaka Prefecture underwent FOBT as one of the items in the comprehensive medical checkups conducted at our Center. These patients were followed up through the end of 1987 by means of record linkage to the Osaka Cancer Registry files in order to identify subsequently diagnosed cancer cases of the esophagus, stomach and colorectum. Results showed that 15 and 3 persons had stomach and colorectal cancer, respectively, diagnosed prior to FOBT. Excluding these cases gave a final cohort of 3,449 examinees.

The results of 2 years' follow-up from FOBT were defined as the gold standard, and sensitivity and specificity of Shionogi A and B slides were calculated for each cancer: true-positive cases were those whose test results had been positive, and for whom cancer was subsequently diagnosed within the next two years, while false-negative cases were those whose test results had been negative, and for whom cancer was subsequently diagnosed within the next two years. In addition, likelihood ratio for a positive test result was calculated for each cancer. In general, this index is defined as sensitivity/(1-specificity) and expresses the odds that a positive test result would be expected in an examinee with (as opposed to one without) the target disease. The 95% confidence intervals (CI) for these three values were calculated according to Simel *et al.*[6]

RESULTS

Table I shows age and sex distributions of the subjects. There were 2,754 males and 695 females. Most of the subjects were between 40 and 69 years of age for both sexes.

Table II presents the results of each test. Four hundred and eighty-two persons (14.0%) showed positive for Shionogi A test and 208 (6.0%) showed positive for Shionogi B test.

Table III shows numbers of subsequently diagnosed cancer cases for each cancer site according to the results of FOBT and the number of years from the testing. For Shionogi A, the numbers of subsequently diagnosed stomach cancer cases were 6 among test positives and 30 among test negatives, and the numbers of colorectal cancer cases were 10 among test positives and 17 among test negatives. For Shionogi B, the numbers of stomach cancer cases were 2 and 34 and those of colorectal cancer were 7 and 20, respectively, for test positives and negatives. For both slides, test positives and test negatives for esophageal cancer numbered 2 and 5, respectively. These numbers are small compared with those for both stomach and colorectal cancer.

Table I. Age and Sex Distributions of Examinees of Occult Blood Tests

Age	Male	Female	Total
–39	274	42	316 (9.2)
40–49	895	161	1,056 (30.6)
50–59	898	317	1,215 (35.2)
60–69	544	153	697 (20.2)
70–	143	22	165 (4.8)
Total	2,754 (79.8)	695 (20.2)	3,449 (100.0) (100.0)

Figures in parentheses are percentages.

Table II. Results of Occult Blood Tests

Result	Test	
	Shionogi A	Shionogi B
Positive	482 (14.0)	208 (6.0)
Negative	2,967 (86.0)	3,241 (94.0)
Total	3,449 (100.0)	3,449 (100.0)

Figures in parentheses are percentages.

When the number of cancer cases was observed by years from the date of FOBT, all the colorectal cancer cases among test positives were diagnosed within 2 years for both slides. However, this was not the case with the distribution of test negative colorectal cancer cases and that of esophageal and stomach cancer cases.

The distribution of clinical stage of stomach cancers diagnosed within two years is shown in Table IV. Of 17 such cases, the numbers of early (mucosal or submucosal) and advanced cancer cases were 10 and 6, respectively, including one unclear cancer case. The number of test positives among advanced cancer cases was only 1 for both slides.

So-called two-by-two tables are shown in Table V, based on the results of Tables II and III according to the above-mentioned definitions of true-positives and false-negatives.

Then, sensitivity, specificity and the likelihood ratio of each slide for each cancer site were calculated and are presented in Table VI. The values of sensitivity for colorectal cancer were 62.5% (CI; 38.8–86.2%) and 43.8% (CI; 19.4–68.1%) for Shionogi A and Shionogi B, respectively. The values of sensitivity for esophageal and stomach cancers were very low as compared with that for colorectal cancer: 20.0% (CI; 0.0–55.1%) and 11.8% (CI; 0.0–27.1%), respectively, for Shionogi A, and 20.0% (CI; 0.0–55.1%) and 5.9%(CI; 0.0–17.1%) for

Table III. Numbers of Subsequently Diagnosed Gastroenterological Cancer Cases by Years of Follow-up and Results of Occult Blood Tests

Years	Test											
	Shionogi A						Shionogi B					
	Esophageal cancer		Stomach cancer		Colorectal cancer		Esophageal cancer		Stomach cancer		Colorectal cancer	
	+	−	+	−	+	−	+	−	+	−	+	−
<1	0	2	0	6	7	3	0	2	0	6	6	4
1–2	1	2	2	9	3	3	1	2	1	10	1	5
2–3	1	1	2	6	0	5	1	1	0	8	0	5
3–4	0	0	1	2	0	2	0	0	0	3	0	2
4–5	0	0	1	2	0	2	0	0	1	2	0	2
>5	0	0	0	5	0	2	0	0	0	5	0	2
Total	2	5	6	30	10	17	2	5	2	34	7	20

Table IV. Distribution of Clinical Stage of Stomach Cancers Diagnosed within 2 Years of Follow-up

Stage of stomach cancer	Test			
	Shionogi A		Shionogi B	
	+	−	+	−
Early	1	9	0	10
Advanced	1	5	1	5
Unknown	0	1	0	1
Total	2	15	1	16

Table V. Two-by-Two Tables by Cancer Site

Test	Esophageal cancer		Stomach cancer		Colorectal cancer	
	+	−	+	−	+	−
Shionogi A						
Positive	1	481	2	480	10	472
Negative	4	2,963	15	2,952	6	2,961
Shionogi B						
Positive	1	207	1	207	7	201
Negative	4	3,237	16	3,225	9	3,232

Shionogi B. The values of likelihood ratio for colorectal cancer were 4.5 (CI; 3.1–6.7) and 7.5 (CI; 4.2–13.2) for Shionogi A and Shionogi B, respectively. The values of likelihood ratio for esophageal and stomach cancers were also very low as compared with that for colorectal cancer: 1.4 (CI; 0.2–8.3) and 0.8 (CI; 0.2–3.1), respectively, for Shionogi A, and 3.3 (CI; 0.6–19.3) and 1.0 (CI; 0.1–6.6) for Shionogi B. Specificity was almost the same for all three cancer sites, being 86% for Shionogi A and 94% for Shionogi B.

Table VI. Diagnostic Validity[a] of Occult Blood Tests by Cancer Site

Test	Esophageal cancer	Stomach cancer	Colorectal cancer
Shionogi A			
Sensitivity (%)	20.0 (0.0–55.1)	11.8 (0.0–27.1)	62.5 (38.8–86.2)
Specificity (%)	86.0 (84.9–87.2)	86.0 (84.9–87.2)	86.3 (85.1–87.4)
Likelihood ratio	1.4 (0.2–8.3)	0.8 (0.2–3.1)	4.5 (3.1–6.7)
Shionogi B			
Sensitivity (%)	20.0 (0.0–55.1)	5.9 (0.0–17.1)	43.8 (19.4–68.1)
Specificity (%)	94.0 (93.2–94.8)	94.0 (93.2–94.8)	94.1 (93.4–94.9)
Likelihood ratio	3.3 (0.6–19.3)	1.0 (0.1–6.6)	7.5 (4.2–13.2)

Figures in parentheses are 95% confidence intervals.
a) Based on results of 2 years' follow-up from the tests.

DISCUSSION

There have been quite a few reported studies on the diagnostic validity of FOBT for detecting colorectal cancers.[7] In addition, several recent studies on this subject have been conducted in relation to actual mass screenings.[8–10]

The diagnostic validity of FOBT for detecting stomach cancers was also examined in several reports in the 1950's and 60's, when its employment as a screening method was attempted in mass screening programs for stomach cancer in Japan.[11, 12] These studies, however, were not based on the results of follow-up of all the examinees, but

only on the observed positive rates among patients known to have or not to have stomach cancer. In addition, FOBT kits used in those days are not the same as those employed today. Thus, it can be said that the diagnostic validity of FOBT currently employed for detecting upper gastroenterological cancers remains unclear. The present study has, for the first time, evaluated the diagnostic validity of chemical occult blood tests for upper gastroenterological cancers as well as colorectal cancers based on the results of follow-up of all the examinees. We found that the sensitivity and likelihood ratio for cancers of the upper gastrointestinal tract were very low compared with cancers of the large bowel.

In general, it is important to identify all prevalent cancer cases with cancer at the time of the screening test (true-positives and false-negatives) by following up all the screenees, in order to correctly estimate the diagnostic validity of a screening test for a certain cancer. This could be easily carried out through a population-based cancer registry.[4, 5] In the present study, this was performed by means of record linkage between the screenees' files and the Osaka Cancer Registry files. Although true-positives are usually detected by way of further work-up examinations, in the present study they were detected by means of record linkage to the Registry files, as well as false-negatives.

The conditions under which FOBT were performed seemed to deviate in some respects from those of usual mass screenings, since our subjects were undergoing comprehensive medical check-ups. Therefore, the following point should be taken into account in application of the results to usual colorectal mass screenings. In mass screenings, feces are usually collected and smeared onto slides by screenees themselves and actual examination at the laboratory tends to take place at least a few days later. In the present study, however, feces were smeared onto slides by clinical technicians and tests were judged with a rather short time-lag. In general, the results of both chemical and immunological FOBT are influenced to some extent by the part and volume of feces collected, as well as the interval elapsed from sampling to completion of the tests, etc.[7] As these factors are likely to be relatively consistent for clinical technicians, but not for screenees themselves, the estimated validity tends to be higher for the former than for the latter. Thus, it is likely that the diagnostic validity for each cancer in actual mass screenings would be lower than the estimated values in the present study.

The values of sensitivity for gastric cancer were 11.8% and 5.9% for Shionogi A and B, respectively, both of which are very low as compared with those for colorectal cancer (62.5% and 43.8%, respectively). Since only 1 case among the 6 advanced gastric cancer cases was positive at the screening for both tests, these tests are likely to be rather insensitive for advanced cancers as well as early ones.

In general, likelihood ratios for positive test results indicate the ratio of the proportion of test positives between screenees with and without the target disorder.[13] The values of likelihood ratio for colorectal cancer were 4.5 and 7.5 for Shionogi A and B, respectively. On the other hand, those for gastric cancer were 0.8 and 1.0, respectively, which are very close to unity. This means that the prevalence of gastric cancer was almost the same between the entire number of screenees and the test positives. Therefore, it was suggested that neither slide is useful for the detection of gastric cancer.

Sensitivity for esophageal cancer was 20.0% and the likelihood ratio was 1.4–3.3, both of which are low compared with the values for colorectal cancer. Although these values are slightly higher than those for gastric cancer, this is probably due to the unreliability of the results caused by the relatively small number of diagnosed esophageal cancer cases. This point should be further examined using a large number of subjects.

It is generally believed that low sensitivity of FOBT for hemorrhage from the upper gastrointestinal tract is due to the fact that human hemoglobin tends to be degraded by gastric and digestive juice and intestinal bacteria. The low sensitivity for esophageal and gastric cancer observed in the present study is in agreement with this.

Values of specificity for colorectal cancer were 86% and 94% for Shionogi A and B, respectively, both of which are rather high compared with most other studies of chemical FOBT.[14, 15] This is possibly due to the diet having been restricted for 3 days before collecting feces in the present study, unlike other studies.

True-positives and false-negatives for each cancer were defined in accord with the gold standard, that is, the results of 2 years' follow-up. This duration was arbitrarily determined by the authors. These definitions were based on the assumption that cancer cases diagnosed within the subsequent 2 years already had preclinical detectable cancer at the screening. If the duration of the preclinical detectable phase is taken as 1 year, the values of sensitivity for colorectal cancer would be 70.0% and 60.0% for Shionogi A and B, respectively, and that for upper gastroenterological cancer would be 0% for both tests. Those values, however, are rather unstable due to the small numbers of cancer cases.

Recently, studies of diagnostic validity of FOBT for colorectal cancer based on the follow-up of all examinees have been reported by Hiwatashi *et al.*,[8] Mandel *et al.*,[9] and Kumanishi *et al.* in co-operation with us.[10] All three groups reported the sensitivity of colorectal cancer screenings by methods employing three consecutive Hemoccult II slides (Smith Kline Diagnostics, Sunnyvale, California) (Hiwatashi *et al.*, Mandel *et al.*), and

three consecutive Shionogi B slides (Kumanishi *et al.*), and the results were 69.2%, 89.3% and 76.9%, respectively. In comparison with these values, the magnitude of sensitivity for both Shionogi A and B slides in the present study was small. This seems primarily due to the difference in completeness of follow-up, the definition of a false-negative case, screening tests employed, etc., as well as there having been only one day for the completion of test slides in the present study.

In the present study, the authors focused on diagnostic validity for detecting cancers without considering hemorrhage from peptic ulcers. However, Miki *et al.* in cooperation with us reported that there was no difference in the prevalence of gastric and duodenal ulcers between test positive screenees and test negative ones, although the FOBT used was an immunological one.[16]

To summarize, our results suggest that chemical FOBT has little ability to detect esophageal and stomach cancers, and therefore, that further work-up examinations of the upper digestive tract in FOBT positives in colorectal cancer screenings are unwarranted in Japan.

In recent years, immunological FOBT specific to human hemoglobin has been developed, and colorectal cancer mass screenings with these tests have been widely conducted in Japan.[2] It should be noted that the estimated diagnostic validity in the present study may possibly be different from that of immunological FOBT. Similar studies of the immunological tests would be desirable in the near future.

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