Efficacy of Screening Program for Colorectal Cancer

Hidenori Nakama

Abstract

A longitudinal study of the reduction in mortality was carried out to evaluate the efficacy of screening for colorectal cancer. A population-based screening program using the fecal occult blood test was conducted from 1982 to 1995 in the small village of Asahi, Nagano, Japan (index area). The efficacy of the screening program was measured by the standardized mortality ratio (SMR) for colorectal cancer. The SMR in the index area was 142 before screening (1968~1981) and 51 during screening (1982~1995). In addition to a significantly lower SMR in the latter period ($P<0.01$), the change in the relative incidence - (D-B)/B, where D is the SMR during screening, and B is the SMR before screening - showed a 64% reduction. The SMR in Asahi was also compared with that in four neighboring villages (control area) not covered by the screening. The SMR in the control area was 133 before and 121 during screening, for a (D-B)/B value of -9%. The reduction in the relative incidence of colorectal cancer was thus significantly higher in the index area than in the control area ($P>0.01$). These results confirm that the screening program conducted in the index area was effective as a preventive community measure in reducing mortality from colorectal cancer, and that the time trend assessment employed here is a useful method for evaluating the efficacy of cancer screening.

Key words: Colorectal cancer, Efficacy of screening, Mortality reduction, Standarized mortality ratio,Time trend assessment

Introduction

According to the Ministry of Health and Welfare, the Japanese mortality rate from colorectal cancer in 2000 was 28.6 per 100,000 population; this figure has increased more than four times in the past 50 years. Because of this increase in mortality the screening program for colorectal cancer by the immunochemical fecal occult blood test has been introduced in many parts of the country. Although evaluating efficacy in cancer screening is very important, carrying out the appraisal of a screening program may not be easy; this is especially the case with the screening for colorectal cancer in Japan as well as in other developed countries.

The author took part in a 14-year screening program for colorectal cancer conducted in the model area in Nagano Prefecture from 1982 to 1995. The present study analyzes the efficacy of this program using fecal occult blood test on the basis of data collected in the model area.

Materials and methods

Operation of the screening examination

The index area in which the screening program was conducted was the farming

village of Asahi, Nagano Prefecture, Japan. When the screening program was started in 1982, the index area had a population of 4298 (2120 males, 2178 females); those aged over 40 years numbered 2177 (1030 males, 1147 females). In the past 14 years no significant change was observed in total population or the number of those aged over 40 years.

The screening examination was conducted each year for the villagers in the index area aged over 40 years. All participants were screened by the fecal occult blood test. In 1982 and 1983 the chemical guaiac slide Shionogi B (Shionogi Pharmaceutical, Japan) was used as the screening test, but since 1984 it has been performed by a combination of several immunochemical methods. The principles of the immunochemical slide Monohaem (Nihon Pharmaceutical, Japan), which was generally used in this screening program, are as follows. First, those being screened were asked to make a thin fecal smear on the test filter paper. If human hemoglobin was present in the fecal sample, there was an antigen-antibody reaction with the monoclonal antibody in the filter paper. The reacted sample was washed to remove components other than hemoglobin, and a color coupler was added. Oxygen dissociated from hydrogen peroxide by the peroxidase-like activity of the human hemoglobin oxidized tetramethyl benzidine, leading to the appearance of green coloration. The test is uncomplicated and the cost per slide for the test (approximately 160 yen) is low. The author has calculated the sensitivity of this test to be 75.0% and the specificity 96.0%.

Subjects who showed a positive reaction in the screening underwent further examination by total colonoscopy or barium enema. If a polyp or cancer was detected in this examination, the subject received endoscopic or surgical treatment. As follow-up management, the results of treatment and outcome were confirmed, and the identification on survival or death was checked especially for cancer cases. At the same time, a follow-up survey on those who showed negative results in the screening test was conducted to evaluate the validity of the screening examination; also, the cases of all colorectal cancer patients/deceased patients in the index area were investigated.

Analysis of the screening examination

Results of screening. Data are presented for the 14-year period in the index area in terms of (a) attendance rate for screening, (b) percentage showing positive reaction on the fecal occult blood testing, (c) percentage receiving secondary screening, (d) detection rate of colorectal polyp, (e) detection rate of colorectal cancer, and (f) frequency of early colorectal cancer. Furthermore, the rate of false-negative results was calculated to evaluate the validity of the screening examination in the index area.

Effect of screening. Calculation of the SMR was used to assess the effect of screening for colorectal cancer. Changes in the index area were compared to nationwide data for the 14-year period before screening (1968-1981) and for that during screening (1982-1995). For these 14-year periods 1974 was taken as the base year before screening and 1988 during it. The total number of deaths due to colorectal cancer was obtained from the vital statistics for the index area.

The SMR in the index area was also compared with that in four neighboring villages not covered by the screening program, which thus served as a control area. Environmental and social conditions were similar between index and control areas, including population structure and medical service (coverage under the National Health Insurance System).

Statistical analysis, except on the SMR, used the x 2 test, with a P value less than 0.05 considered statistically significant. The SMR was analyzed assuming a Poisson distribution and, again, taking a P value less than 0.05 as statistically significant.

Results

Results of screening

The number of those undergoing screening are presented in Table 1 by sex and age cohort (some were screened more than once). The overall female to male ratio was 1.2; the age distribution did not differ by sex. In 1982 when the colorectal screening was initiated 1771 (81.4%) of the 2177 persons aged over 40 years underwent the screening. The average percentage of those examined over the 14-year period was 54.0%. In 1982 there were 210 subjects (11.9%) who showed positive reactions on the fecal occult blood test. This percentage varied over the years and showed a 10-year average of 4.8%. A highly sensitive chemical guaiac slide was used in 1982-1983, and, in addition, an enzyme-linked immunosorbent assay with this test was in 1984-1985; during this time the positive rate was particularly high. From 1986 this was replaced by immunochemical methods with suitable cutoff point, and this was associated with a relatively low positive rate. Secondary screening was given to 190 subjects (90.5%) in 1982; the 14-year average was 83.1% (73.2%-90.5%; Table 2). In 93.9% the secondary screening was total colonoscopy.

Colorectal polyp was detected in 26 subjects (1.5%) in the initial year of screening, and the detection rate decreased slowly in the subsequent years. Colorectal cancer was detected in 4 subjects (0.2%) in 1982 and in 21 over the entire 14-year period. Of these 21 cases 17(80.9%) were of early cancer. After 1985 only early cancer was detected (Table 3). In the 14-year period six cases of colorectal cancer were detected outside the screening examination. Three of these subjects had been evaluated as normal by the screening examination but were later diagnosed in outpatient clinics as having colorectal cancer. The rate of false-negative results was 12.5%.

Effect of screening

The SMR in the 14-year period before (B) screening was 142.1 and that in the 14-year period during screening (D) was 51.1 ($P<0.01$). The change in relative incidence rate, calculated as (D-B)/B, shows a reduction of 64.1% (Table 4). The SMR in the control area was 132.8 in the former period and 121.4 in the latter (NS). The relative incidence rate here shows a 8.9% reduction. The difference in the reduction between the index and control areas was statistically significant ($P<0.01$; Table 4).

Discussion

In Japan a Health and Medical Service Law for the Aged was enacted in 1982 which encouraged those aged over 40 years to receive cancer screening. This law provides for the screening of stomach, uterus, lung, and breast cancer and is considered to have contributed to the early detection of cancer and to the lowering of cancer mortality. Due to the recent increase in mortality from colorectal cancer in Japan, a screening program for colorectal cancer was introduced by the Ministry of Health and Welfare in 1992.

The International Union Against Cancer has organized a number of workshops since 1978 and has issued guidelines for executing cancer screening, with specific emphasis on the need to confirm the mortality-lowering effect of screening before introducing it as a public health policy. The United States Task Force for Preventive Service has issued a similar statement, maintaining that the introduction of cancer screening could not be recommended until the mortality-lowering effect of the examination is verified.

The present study was carried out to test the hypothesis that annual colorectal screening using the fecal occult blood test lowers the population risk for mortality from colorectal cancer. The SMR of colorectal cancer in our index area was higher before screening than during screening. Comparison of the SMR in the index area with that in the control area also confirmed the SMR-reducing effect of the screening program.

It is widely considered that the randomized controlled trial (RCT) is the best means by which to examine the validity of mass screening. RCTs using the fecal occult blood test for colorectal cancer has verified the screening effect in mortality reduction. Carrying out an RCT entails numerous problems, and its institution in Japan cannot be considered feasible. Furthermore, very few research reports have verified the efficacy of screening for colorectal cancer. Various types of methodology must therefore be examined for the study of a possible screening effect.

The author conducted a comparative study evaluating the screening effect and reported in a separate paper that detection of the clinical stage and improvement in the survival rate show advantages of screening over reliance on outpatient clinics.

The present study was carried out to evaluate the efficacy of cancer screening in regard to reducing mortality.

RCTs seek to minimize the problems of bias in epidemiological studies, which cannot be solved in nonrandomized studies. A basic principle of epidemiological studies is consistency in design and methods, and when this is assured, the results of such studies are more reliable. The longitudinal method used in the present study to assess mortality confirms the epidemiological efficacy of mass screening programs for colorectal cancer using fecal occult blood test.

References

1. Chamberlain J, Day N, Hakama M, Miller AB, prorok PC (1986) UICC workshop of the project on evaluation of screening programmes for gastrointestinal cancer. Int J Cancer 37:329-338
2. Cole P, Morrison AS (1980) Basic issues in population screening for cancer. J Natl Cancer Inst 64:1263-1272
3. Faivre J (1989) Preliminary result of a mass screening programme for colorectal cancer in France. In: Hardcastle JD (ed) Screening for colorectal cancer. Normed, Engelwood, pp 94-101
4. Gilberten VA, Church TR, Grewe FJ (1980) The design of a study to assess occult-blood screening for colon cancer. J Chronic Dis 3:107-114
5. Hanai A, Fujimoto I (1990) Population-based cancer registries in Japan. In: Sasaki R, Aoki K (ed) Epidemiology and prevention of cancer. University of Nagoya Press, Nagoya, pp 199-204
6. Hardcastle JD, Armitage NC, Chamberlain J, Amar SS, James PD, Balfour TW (1986) Fecal occult blood screening for colorectal cancer in the general population. Cancer 58:397-404
7. Hardcastle JD, Chamberlain JO, Robinson MHE (1996) Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 348:1472-1477
8. Kewenter J, Bjoke S, Hanglind E, Smith L, Svanvik J, Ahren C (1988) Screening and rescreening for colorectal cancer: a controlled trial of faecal occult blood testing in 27700 subjects. Cancer 62:645-651
9. Kewenter J, Asztely M, Engaras B, Hanglind E, Svanvik J, Ahren C (1991) A randomised trial of faecal occult blood testing for early detection of colorectal cancer: results of screening and rescreening of 51,325 subjects. In: Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC (eds) Cancer screening. Cambridge University Press, Cambridge, pp 117-125
10. Knight K, Fielding JE, Batlista R (1989) Occult blood screening for colorectal cancer. JAMA 21:586-593
11. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O(1996) Randomised

study of screening for colorectal cancer with faecal-occult-blood test. Lancet 348:1467-1471
12. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schumax LM, Ederer F (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 328:1365-1371
13. Moss SM (1991) Case-control studies of screening. Int J Epidemiol 20:1-6
14. Nakama H(1994) A study on the efficacy of a screening program for colorectal cancer in a small Japanese village. Clin Investig 72:117-121
15. Nakama H (1994) Acomparatine study on the efficacy of a mass screening program for colorectal cancer - comparison between cancer cases detected by mass screening and by outpatientclinics. Asia Pac J Public Health 7:159-164
16. Nakama H, Kamijo N(1994) Accuracy of the immunological fecal occult blood testing for colorectal cancer screening. Prev Med 23:309-313
17. Nakama H, Kamijo N, Fattah ASMA, Zhang B(1996) Validity of immunological faecal occult blood screening for colorectal cancer screening: a follow-up study. J Med Screen 3:63-65
18. Nakama H, Kamijo N, Fujimori K, Fattah ASMA, Zhang B (1996) Diagnostic accuracy of immunochemical faecal occult blood test for gastric cancer. J Med Screen 3:113-114
19. Nakama H, Kamijo N, Fujimori K, Horiuchi A, Fattah ASMA, Zhang B (1997) Immunochemical fecal occult blood test is not suitable for diagnosis of hemorrhoids. Am J Med 102:551-554
20. Nakama H, Kamijo N, Fattah ASMA, Zhang B (1998) Immunochemical detection of fecal occult blood from upper digestive tract diseases. Hepatogastroenterology 45:752-754
21. Nakama H, Kamijo N, Miyata K, Fattah ASMA, Zhang B, Uehara Y (1998) Sensitivity and specificity of several immunochemical tests for colorectal cancer screening. Hepatogastroenterology 45:1579-1582
22. Nakama H, Yamamoto M, Kamijo N, Fattah ASMA, Zhang B (1999) Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. Hepatogastroenterology 46:228-231
23. Nakama H, Zhang B, Fukazawa K, Fattah ASMA (2000) Family history of colorectal adenomatous polyps as a risk factor for colorectal cancer. Eur J Cancer 36:2111-2114
24. Nakama H, Zhang B, Fukazawa K (2000) Colorectal cancer screening under age of 50 is less cost-effective. GI Cancer 3:371-374
25. Nakama H, Zhang B, Fattah ASMA, Kamijo N, Fukazawa K (2000) Relationships between a sign of rectal bleeding and the results of an immunochemical occult blood test, and colorectal cancer. Eur J Cancer Prev 9:325-328
26. Nakama H, Zhang B, Fukazawa k, Zhang X (2001) Comparisons of cancer detec-

tion rate and costs for one cancer detected among different age-cohorts in immunochemical occult blood screening. J Cancer Res Clin Oncol 127:439-443
27. Nakama H, Zhang B, Zhang. B (2001) Evaluation of optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. Eur J Cancer 37:398-401
28. Nakama H, Zhang B, Fattah ASMA, Kamijo N, Zhang X (2001) Characterisitics of colorectal cancer that produce positive immunochemical occult blood test results on stool obtained by digital rectal examination. Can J Gastroenterol 15:227-230
29. Nakama H, Zhang B, Fattah ASMA, Kamijo N (2001) Does stool collection method affect outcomes in immunochemical fecal occult blood testing. Dis Colon Rectum 44:871-875
30. Nakama H, Zhang B (2002) Colorectal cancer risk in first-degree relatives of patients with colorectal adenomatous polyp. Hepatogastroenterology 49:165-167
31. Nakama H, Zhang B (2002) Lower specificity of occult-blood test on stool collected by digital rectal examination. Hepatogastroenterology 49:165-167
32. Oshima A, Hirata H, Ubukata T, Fujimoto I (1986) Evaluation of a mass screening program for stomach cancer with a case-control study design. Int J Cancer 38:829-833
33. Ota J, Horino T, Taguchi T, Ishida T, Izuo M, Ogita M (1989) Mass screening for breast cancer: comparison of the clinical stages and prognosis of breast cancer detected by mass screening and in out-patient clinics. Jpn J Cancer Res 80:1028-1034
34. Robra B, Wahrendorf J (1989) Fecal occult blood screening in the Federal Republic of Germany. In: Hardcastle JD (ed) Screening for colorectal cancer. Normed, Engelwood, pp 107-114
35. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS (1992) A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 326:53-57
36. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS (1993) Effect of fecal occult blood testing on mortality from colorectal cancer. Ann Int Med 118:1-6
37. Sobue T, Suzuki T, Hashimoto S, Yokoi N, Fujimoto I (1988) A case-control study of effectiveness of cervical cancer screening in Osaka, Japan. Jpn J Cancer Res 79:1269-1275
38. Statistics and Information Department (2002) Vital statistics, 2000 Japan, Vol 49. Minister's Secretariat, Ministry of Health and Welfare, Tokyo, p390
39. Winawer SJ, Schottenfeld D, Flehinger BJ (1991) Colorectal cancer screening. J Natl Cancer Inst 83:243-253

Table 1. Age and sex distribution of those screened

Age (years)	Sex		Female/Male
	Male	Female	
40-49	1123	1357	1.2
50-59	1404	1767	1.3
60-69	2059	2200	1.1
70-79	1041	1182	1.1
80+	83	95	1.1
Total	5710	6610	1.2 (Av.)

Table 2. Results of screening program

Year	Subjects (n)	Screened		Positive cases		Examinedes	
		n	% of subjects	*n*	% of screened	*n*	% of pos. cases
1982	2177	1771	81.4	210	11.9	190	90.5
1983	2204	1376	62.4	153	11.1	112	73.2
1984	2155	1241	57.6	145	11.7	109	75.2
1985	2139	1306	61.1	185	14.2	131	70.8
1986	2236	1257	56.2	115	9.1	103	89.6
1987	2236	1106	49.5	59	5.3	50	84.7
1988	2094	1130	54.0	81	7.2	69	85.2
1989	2106	1070	50.8	89	8.3	76	85.4
1990	2127	1064	50.0	45	4.2	39	86.7
1991	2098	990	47.2	54	5.5	45	83.3
1992	2123	1012	47.7	48	4.7	41	85.4
1993	2170	898	41.4	39	4.3	32	82.1
1994	1571	846	53.9	38	4.5	30	78.9
1995	1427	594	41.6	31	5.2	27	87.1
Total	28863	12311	54.0	1292	7.7	1054	82.7

Table 3. Colorectal polyps and cancers detected by the screening program: number, and percentage of those screened (S%), positive cases (P%), and those examined (E%)

Year	Colorectal polyps				Colorectal cancers				
	n	S%	P%	E%	*n*	Early cases	S%	P%	E%
1982	26	1.5	12.4	13.7	4	3	0.2	1.9	2.1
1983	15	1.1	9.8	13.4	1	0	0.1	0.7	0.9
1984	13	1.0	9.0	11.9	2	0	0.2	1.4	1.8
1985	15	1.1	8.1	11.5	4	4	0.3	2.2	3.1
1986	12	1.0	10.4	11.7	4	4	0.3	3.5	3.9
1987	10	0.9	16.9	20.0	1	1	0.1	1.7	2.0
1988	8	0.7	9.9	11.6	0	0	0.0	0.0	0.0
1989	7	0.7	7.9	9.2	0	0	0.0	0.0	0.0
1990	7	0.7	15.6	17.9	1	1	0.1	2.2	2.6
1991	5	0.5	9.3	11.1	1	1	0.1	1.9	2.2
1992	4	0.4	8.3	9.8	1	1	0.1	2.1	2.4
1993	6	0.7	15.4	18.8	1	1	0.1	2.6	3.1
1994	7	0.8	18.4	23.3	0	0	0.0	0.0	0.0
1995	6	1.0	19.4	22.2	1	1	0.2	3.2	3.7
Total	141	1.0	11.0	13.2	21	17	0.1	1.7	1.9

Table 4. SMR for colorectal cancer 1972-1981 (B) versus 1982-1991 (D) in the index and control areas and change in relative incidence

	SMR		
	1972-1981	1982-1991	(D-B)/B
Index area	142.1	51.1	64.1% *
		*	
Control area	132.8	121.4	-8.6% *

* $P < 0.01$