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Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: A prospective cohort study in Japan

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for the Japan Public Health Center-based Prospective Study[1]

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Abstract

Background: To investigate prospectively the association between colorectal cancer screening and subsequent risk of colorectal cancer death in a large-scale population-based cohort study (the JPHC study) with a 13-year follow-up period in Japan. *Methods*: We analyzed data from a population-based cohort of 42,150 (20,326 men and 21,824 women) subjects. Subjects who had undergone fecal occult blood test (FOBT) screening during the preceding 12 months were defined as the screened group. A total of 132 colorectal cancer deaths and 597 cases of newly diagnosed colorectal cancer were identified during the follow-up period. *Results*: We observed a nearly 70% decrease in colorectal cancer mortality in screened versus unscreened subjects (RR = 0.28, 95% CI = 0.13–0.61). Screening participation was associated with a 30% reduced risk of death from all causes other than colorectal cancer (RR = 0.70, 95% CI = 0.61–0.79). However, the extent of mortality reduction was greater for colorectal cancer than other causes. A significant decrease in the incidence of advanced colorectal cancer was seen in screened subjects (RR = 0.41, 95% CI = 0.27–0.63), although the overall incidence rate did not differ significantly between the screened and unscreened groups. *Conclusion*: Although self-selection bias could not be fully controlled, these findings suggest that colorectal cancer screening may be associated with a reduction in mortality from colorectal cancer in the Japanese population.
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Keywords: Colorectal cancer; Colorectal cancer Screening; FOBT; Prospective study; Japan; Lifestyle; Dietary factors; Education level; Exposure assessment; 13-year follow-up period; Statistical analysis

1. Introduction

Colorectal cancer ranks as the second most common cancer by incidence and the second leading cause of cancer mortality in more developed countries, with nearly 945,000 new cases of colorectal cancer diagnosed worldwide each year and 492,000 deaths [1]. In Japan, the incidence and mortality of colorectal cancer has recently increased, with 36,000 deaths in 2000 [2].

Although colorectal cancer is considered to be closely related to environmental factors, particularly diet and lifestyle, effective methods for primary prevention have yet to be established [3]. The best near-term option for decreasing the burden of colorectal cancer is therefore screening for early cancer and precancerous lesions. Among several modalities that have been proposed for colorectal cancer screening, the fecal occult blood test (FOBT) or Hemoccult test has been demonstrated in three landmark randomized controlled trials to reduce mortality from this cancer by 15–33% [4–7]. It is nevertheless acknowledged that the specificity and sensitivity of fecal occult blood screening are limited [1].

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In Japan, immunochemical FOBT developed for use in mass screening in 1983 has been recommended as a screening test for colorectal cancer by the Japanese Society of Gastroenterological Mass Survey [8]. A national survey conducted in 1988 indicated that an immunochemical test was already used in more than 92% of screening FOBTs in Japan [8]. Colorectal cancer screening program using this test was started in Aomori Prefecture, Japan in 1986, and screening was incorporated into public health policy in 1992. It was subsequently expanded and is now an established cancer control strategy nationwide [9,10]. National statistics indicate that 6 million inhabitants, representing 17% of those aged 40 years or over, participated in colorectal cancer screenings organized by local governments in 2002 [11]. It has been proposed that flexible sigmoidoscopy and double contrast barium enema or colonoscopy are recommended if a positive FOBT is obtained [8,10].

Although randomized controlled trials represent the most reliable method for evaluating the impact of screening on cancer risk, the national screening system means this option is not available for colorectal cancer in Japan. Efficacy has therefore been assessed using other epidemiological methods [9,10,12–14], but to date no prospective results have been obtained.

The aim of the present study was to prospectively investigate the association between colorectal cancer screening and the subsequent risk of colorectal cancer death in the Japanese population using a large-scale population-based prospective cohort study with a 13-year follow-up period.

2. Materials and methods

2.1. Study population and baseline survey

The basis for this investigation lies with the Japan Public Health Center-based prospective study (JPHC Study) Cohort I, which was established in January 1990 and included questions on screening experience in the baseline survey. The Cohort covered five prefectural public health center (PHC) areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo). Details of the study design have been provided elsewhere [15]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. For the present analysis, the Katsushika PHC area was excluded since its study population was defined differently to the others, and no data for cancer incidence were available. The study population was defined as all registered Japanese inhabitants of 14 administrative districts supervised by the 4 PHC areas aged 40–59 years at the beginning of the baseline survey. The Japanese inhabitants were identified from population registries maintained by the local municipalities. Initially, 54,498 subjects were identified as the study population. Of these, 121 were found to be ineligible during the follow-up period and excluded for any of several reasons (non-Japanese nationality ($n = 29$), late report of emigration occurring before the start of the follow-up period ($n = 86$), incorrect birth date ($n = 3$), and duplicate data ($n = 3$)), giving a final population-based cohort of 54,377 subjects (26,988 men and 27,389 women).

A baseline self-administered questionnaire survey, which included socio-demographics, personal medical history, screening experience, smoking and alcohol drinking history, and diet, was conducted in 1990. A total of 43,140 subjects responded, giving a response rate of 79%. We further excluded 990 subjects with a present or past history of cancers (e.g. colorectal, gastric, lung, liver, breast, uterine, and other cancer) at baseline. Finally, 42,150 eligible subjects (20,326 men and 21,824 women) were included in the analysis.

2.2. Follow-up

Subjects were followed from the baseline survey until 31 December 2003. Residence status was confirmed annually through the residential registry maintained by the respective study area municipalities; for those who moved out of the area, residence status was confirmed through the municipal office of the area to which they had moved. The registration of deaths in Japan is required by the Family Registration Law and the registry is believed to be complete. Inspection of the resident registry is available to anyone under the Resident Registration Law. Information on the cause of each death was supplemented by checking against death certificate files provided by the Ministry of Health, Labor, and Welfare after permission was obtained from the Ministry of Internal Affairs and Communications. We classified the causes of death according to the International Classification of Diseases, 10th Revision (ICD10) as follows: deaths from colorectal cancer (ICD10: C18-C20), all cancers (ICD10: C00-C97) [16]. Those already coded according to the ICD 9th Revision (1990–1994) were converted into ICD10 code. During the study period, 2678 subjects died, 2791 moved out of the study area (7%), and 58 were lost to follow-up (0.1%). Among the study subjects, 132 died of colorectal cancer during the follow-up period.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from each of the local governments responsible for the cancer registries. Death certificate information was used as a supplementary information source. The site and histology of each case were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [17]. As of December 2003, a total of 597 newly diagnosed colorectal cancer cases were identified based on ICD-O-3 (code: C18-C20). Finally, 42,150 subjects (20,326 men and 21,824 women) were used for analysis, including

132 colorectal cancer deaths and 597 incident colorectal cancers.

2.3. Exposure and outcome

Information on screening FOBT was obtained from the subjects' self-reported screening experience, using the questionnaire in the two categories of yes (i.e. has undergone screening) and no. Subjects were also asked about the screening method they had undergone. The conceptual definition of the screened group was those who had undergone FOBT screening at baseline. Therefore, those who reported undergoing FOBT screening during the 12 months preceding the baseline survey were defined as the screened group. Colorectal cancer death (ICD10: C18-C20, C18 (colon) and C19-C20 (rectum)) was the main outcome. Additional outcome variables were incident colorectal cancer (ICD-O-3: C18-C20, C18 (colon) and C19-C20 (rectum)), death from all cancers (ICD10: C00-C97) except colorectal cancer, death from all causes except colorectal cancer, and incident cases of all cancers other than colorectal cancer.

2.4. Statistical analysis

Person-years were counted from the date of response to the baseline survey until one of the following endpoints: for the analysis of colorectal cancer deaths, the date of emigration from the study area, the date of death, or the end of the study period (31 December 2003), whichever came first; and for the analysis of colorectal cancer incidence, the date of occurrence of colorectal cancer, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. Persons who were lost to follow-up were censored on the last confirmed date of their presence in the study area.

Colorectal cancer death was the main outcome measure. To evaluate potential selection bias, death from all cancers other than colorectal cancer, all causes of death excluding colorectal cancer, and incident cases of colorectal cancer and of all cancers other than colorectal cancer were used as additional outcome variables. To estimate the incidence rate of advanced colorectal cancer, incident cases invading into the muscularis propriae or deeper, that is, T2–T4 in the TNM Classification, were considered as advanced cancer cases [18,19]. The risk of incidence of advanced colorectal cancer was compared with that of nonadvanced colorectal cancer incidence after excluding 37 cases that had no information on the classification. Relative risk (RR) and 95% confidence intervals (95% CI) were used to describe the relative risk of colorectal cancer death and the incidence associated with colorectal cancer screening. Subgroup analyses were done to investigate the effect of screening in men and women. Additional age-stratified analyses were done to investigate the effect of screening in subjects aged 40–49 and 50–59 years, and their respective RRs were estimated. Subsite-stratified analyses were also done, and their respective RRs estimated.

Differences in proportions and mean values among the screened and unscreened subjects were assessed using the Chi-square test and unpaired *t*-test, respectively. The Cox proportional hazards regression model was used to control potential confounding factors. We adjusted for age at baseline (continuous), sex and study area (four PHC areas), then further adjusted for educational background (up to high school, college or higher), smoking status (never, former, or current), alcohol intake (none, occasional, or regular), family history of colorectal cancer (yes or no), body mass index (continuous), physical exercise (less than once per month, 1–3 times per month, more than once per week), green-yellow vegetable intake (everyday, less than everyday), beef intake (at least three times per week, or less), and pork intake (at least three times per week, or less). In women, additional adjustment was also made for use of hormone replacement therapy. These variables are either known or suspected risk or preventive factors for colorectal cancer [20–27]. Besides, we additionally adjusted for screening histories for hypertension, gastric cancer and lung cancer. To avoid the potential effects of past screenings, all analyses were repeated after subjects diagnosed with or dying of colorectal cancer during the first 3 years of the follow-up period were excluded. The significance of interactions between the screening and these risk factors for colorectal cancer was determined by comparing the model of the screening × the respective variable with the model that assessed the main effect only. Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

3. Results

During the 551,459 person-years of follow-up (average follow-up period: 13.1 years) for 42,150 subjects (20,326 men and 21,824 women), a total of 132 colorectal cancer deaths and 597 cases of newly diagnosed colorectal cancer were identified and included in the analyses.

Baseline characteristics of subjects according to colorectal cancer screening using FOBT are shown in Table 1. Overall mean age was 49.5 years and mean body mass index was 23.6 kg/m^2. At baseline, approximately 17% had undergone colorectal cancer screening during the preceding 12 months. The educational level of the screened group was higher than that of the unscreened group. Current smokers were more common in the unscreened group, but regular drinkers were more common in the screened group. The screened subjects were more likely than the unscreened subjects to favor green-yellow vegetables, pork and fish and less likely to consume beef, but were also more likely to report a family history of colorectal cancer. Frequent physical exercise was more common in the screened than in the unscreened subjects.

Table 1
Baseline characteristics of study subjects according to colorectal cancer screening

	Unscreened (n = 34,971)	Screened (n = 7179)	p
Proportion (%)	82.97	17.03	
Mean age (years) ± S.D.	49.4±5.9	50.3 ± 5.8	<0.0001[a]
Body mass index (kg/m^2)			
Mean ± S.D.	23.6 ± 3.1	23.5 ± 3.0	0.0253[a]
Sex (%)			
Male	48.07	48.98	
Female	51.93	51.02	0.1609[b]
Educational level (%)			
≤12 years of schooling	87.38	84.38	
>12 years of schooling	12.62	15.62	<0.0001[b]
Smoking status (%)			
Never	59.48	60.00	
Former	11.34	14.24	
Current	29.18	25.75	<0.0001[b]
Alcohol drinking status (%)			
None	51.31	45.83	
Occasional	11.30	12.16	
Regular	37.38	42.02	<0.0001[b]
Family history of colorectal cancer (%)			
No	99.16	98.54	
Yes	0.84	1.46	<0.0001[b]
Beef intake (%)			
<3 times per week	88.68	90.27	
≥3 times per week	11.32	9.73	0.0001[b]
Pork intake (%)			
<3 times per week	68.29	64.76	
≥3 times per week	31.71	35.24	<0.0001[b]
Fish intake (%)			
<3 times per week	47.85	45.63	
≥3 times per week	52.15	54.37	0.0006[b]
Chicken intake (%)			
<3 times per week	73.24	73.77	
≥3 times per week	26.76	26.23	0.3601[b]
Green-yellow vegetable intake (%)			
Less than everyday	61.69	58.34	
Everyday	38.31	41.66	<0.0001[b]
Rice intake (%)			
<4 bowls per day	70.29	70.24	
≥4 bowls per day	29.71	29.76	0.9285[b]
Physical exercise (%)			
Less than once per month	74.40	62.87	
One to three times per month	10.59	16.63	
More than once per week	15.02	20.50	<0.0001[b]

[a] By unpaired t-test.
[b] By χ^2-test.

Table 2
Relative risk and 95% confidence interval for colorectal cancer screening and subsequent risk of colorectal cancer in 42,150 subjects in the JPHC Study[a]

	Unscreened	Screened
Deaths		
Person-years of follow-up	456520.0	94938.6
Colorectal cancer (n = 132)		
Number of deaths	124	8
RR (95% CI)[b]	1.00 (reference)	0.29 (0.14–0.59)
RR (95% CI)[c]	1.00 (reference)	0.28 (0.13–0.61)
RR (95% CI)[d]	1.00 (reference)	0.31 (0.14–0.69)
All cancers excluding colorectal cancer (n = 1009)		
Number of deaths	856	153
RR (95% CI)[b]	1.00 (reference)	0.79 (0.67–0.94)
RR (95% CI)[c]	1.00 (reference)	0.82 (0.68–0.99)
RR (95% CI)[d]	1.00 (reference)	0.91 (0.75–1.11)
All causes of death excluding colorectal cancer (n = 2546)		
Number of deaths	2214	332
RR (95% CI)[b]	1.00 (reference)	0.67 (0.60–0.76)
RR (95% CI)[c]	1.00	0.70 (0.61–0.79)
RR (95% CI)[d]	1.00	0.80 (0.70–0.91)
Incidence		
Person-years of follow-up	434403.1	89741.1
Colorectal cancer[e] (n = 597)		
Number of cases	502	95
RR (95% CI)[b]	1.00	0.87 (0.69–1.08)
RR (95% CI)[c]	1.00	0.82 (0.65–1.04)
RR (95% CI)[d]	1.00	0.82 (0.64–1.05)
Nonadvanced CRC[f] (n = 260)		
Number of cases	199	61
RR (95% CI)[b]	1.00 (reference)	1.38 (1.03–1.84)
RR (95% CI)[c]	1.00 (reference)	1.34 (0.99–1.81)
RR (95% CI)[d]	1.00 (reference)	1.16 (0.84–1.60)
Advanced CRC[g] (n = 300)		
Number of cases	273	27
RR (95% CI)[b]	1.00 (reference)	0.46 (0.31–0.68)
RR (95% CI)[c]	1.00 (reference)	0.41 (0.27–0.63)
RR (95% CI)[d]	1.00 (reference)	0.44 (0.28–0.69)
All cancers excluding colorectal cancer (n = 2474)		
Number of cases	1986	488
RR (95% CI)[b]	1.00 (reference)	1.11 (1.00–1.22)
RR (95% CI)[c]	1.00 (reference)	1.12 (1.00–1.24)
RR (95% CI)[d]	1.00 (reference)	1.12 (1.00–1.25)

[a] RR, relative risk; CI, confidence interval.
[b] Adjusted for age at baseline, sex and study area.
[c] Additionally adjusted for smoking status, alcohol intake, educational level, family history of colorectal cancer, body mass index, green-yellow vegetable, beef, and pork intake, and physical exercise.
[d] Further adjusted for health check-ups for blood pressure and stomach and lung cancer screening.
[e] Overall incidence rate of colorectal cancer.
[f] Incidence of nonadvanced colorectal cancer.
[g] Incidence of advanced colorectal cancer.

The relative risk for subsequent risk of colorectal cancer according to colorectal cancer screening is shown in Table 2. The screened subjects showed a 72% reduced risk of death from colorectal cancer compared with the unscreened subjects (RR = 0.28, 95% CI = 0.13–0.61). Screening participation was associated with a 30% reduced risk of death from all causes other than colorectal cancer (RR = 0.70, 95% CI = 0.61–0.79). However, the extent of mortality reduction was greater for colorectal cancer than for

other causes. This trend did not change when cases of death from colorectal cancer occurring within the first 3 years of the follow-up period were excluded (for colorectal cancer death, RR = 0.31, 95% CI = 0.14–0.67; for death from all causes other than colorectal cancer, RR = 0.70, 95% CI = 0.61–0.79). Although the overall incidence of colorectal cancer did not differ significantly between the screened and unscreened groups, a significant decrease in the incidence of advanced colorectal cancer was seen in the screened subjects (RR = 0.41, 95% CI = 0.27–0.63). No significant difference in the incidence of nonadvanced colorectal cancer was seen between the screened and unscreened groups (RR = 1.34, 95% CI = 0.99–1.81). Similarly, this trend was not changed after the exclusion of colorectal cancer cases occurring within the first 3 years of follow-up (RR = 0.41, 95% CI = 0.26–0.65; RR = 1.34, 95% CI = 0.97–1.86). Moreover, these tendencies were not changed after further adjustments for screening histories for hypertension, gastric cancer and lung cancer (for colorectal cancer death, RR = 0.31, 95% CI = 0.14–0.69; for all causes death other than colorectal cancer, RR = 0.80, 95% CI = 0.70–0.91; for incidence of advanced colorectal cancer, RR = 0.44, 95% CI = 0.28–0.69). The rate of decline in mortality rate was greater than that in incidence rate among the screened subjects.

The subgroup analyses were based on only a few deaths in each strata since the number of deaths from colorectal cancer in the screened group was small. Analyses of the subgroups revealed a significantly reduced risk of death from colorectal cancer in a similar proportion in men and women (for men, RR = 0.28, 95% CI = 0.10–0.76; for women, RR = 0.21, 95% CI = 0.05–0.85). Screening participation was associated with a significantly reduced risk of death from all causes other than colorectal cancer in men (RR = 0.65, 95% CI = 0.56–0.76), but the extent of mortality reduction was greater for colorectal cancer than for other causes. This trend in decreased death from colorectal cancer did not change after the first 3 years of the follow-up period were excluded (for men, RR = 0.29, 95% CI = 0.11–0.81; for women, RR = 0.23, 95% CI = 0.06–0.96). Although the overall incidence rate of colorectal cancer did not differ significantly between the screened and unscreened groups, a significant decrease in the incidence of advanced colorectal cancer was seen in the screened compared with the unscreened men (RR = 0.29, 95% CI = 0.15–0.55). Similarly, no substantial change in these trends was seen even after further adjustments for other screening history (Table 3).

Additional investigation of the interaction between colorectal cancer screening and age group revealed borderline significant interaction effects ($p = 0.056$), leading us to investigate the association between colorectal cancer screening and subsequent risk of colorectal cancer using the age-stratified analyses (Table 4). The screened subjects showed a 77% reduced risk of death from colorectal cancer in those aged 50–59 years at baseline

Table 3
Relative risk and 95% confidence interval for colorectal cancer screening and subsequent risk of colorectal cancer according to sex in the JPHC Study[a]

	Unscreened	Screened
Men ($n = 20,326$)		
Cancer deaths		
Person-years of follow-up	216436.7	45904.2
Colorectal cancer ($n = 75$)		
Number of deaths	70	5
RR (95% CI)[b]	1.00 (reference)	0.31 (0.13–0.77)
RR (95% CI)[c]	1.00 (reference)	0.28 (0.10–0.76)
RR (95% CI)[d]	1.00 (reference)	0.30 (0.11–0.84)
Cancer incidence		
Person-years of follow-up	205211.4	42941.1
Colorectal cancer[e] ($n = 370$)		
Number of cases	314	56
RR (95% CI)[b]	1.00 (reference)	0.81 (0.61–1.08)
RR (95% CI)[c]	1.00 (reference)	0.78 (0.58–1.06)
RR (95% CI)[d]	1.00 (reference)	0.77 (0.56–1.05)
Nonadvanced CRC[f] ($n = 176$)		
Number of cases	138	38
RR (95% CI)[b]	1.00 (reference)	1.23 (0.86–1.77)
RR (95% CI)[c]	1.00 (reference)	1.26 (0.87–1.83)
RR (95% CI)[d]	1.00 (reference)	1.08 (0.73–1.60)
Advanced CRC[g] ($n = 177$)		
Number of cases	165	12
RR (95% CI)[b]	1.00 (reference)	0.33 (0.18–0.60)
RR (95% CI)[c]	1.00 (reference)	0.29 (0.15–0.55)
RR (95% CI)[d]	1.00 (reference)	0.32 (0.16–0.61)
Women ($n = 21,824$)		
Cancer deaths		
Person-years of follow-up	240083.3	49034.4
Colorectal cancer ($n = 57$)		
Number of deaths	54	3
RR (95% CI)[b]	1.00 (reference)	0.26 (0.08–0.82)
RR (95% CI)[h]	1.00 (reference)	0.21 (0.05–0.85)
RR (95% CI)[d]	1.00 (reference)	0.24 (0.06–1.00)
Cancer incidence		
Person-years of follow-up	229191.7	46800.0
Colorectal cancer[e] ($n = 227$)		
Number of cases	188	39
RR (95% CI)[b]	1.00 (reference)	0.97 (0.68–1.37)
RR (95% CI)[h]	1.00 (reference)	0.88 (0.60–1.29)
RR (95% CI)[d]	1.00 (reference)	0.91 (0.61–1.35)
Nonadvanced CRC[f] ($n = 84$)		
Number of cases	61	23
RR (95% CI)[b]	1.00 (reference)	1.73 (1.07–2.80)
RR (95% CI)[h]	1.00 (reference)	1.52 (0.91–2.55)
RR (95% CI)[d]	1.00 (reference)	1.33 (0.77–2.31)
Advanced CRC[g] ($n = 123$)		
Number of cases	108	15
RR (95% CI)[b]	1.00 (reference)	0.65 (0.38–1.13)
RR (95% CI)[h]	1.00 (reference)	0.60 (0.33–1.07)
RR (95% CI)[d]	1.00 (reference)	0.62 (0.34–1.14)

[a] RR, relative risk; CI, confidence interval.
[b] Adjusted for age at baseline and study area.
[c] Adjusted for age, study area, smoking status, alcohol intake, educational level, family history of colorectal cancer, body mass index, green-yellow vegetable, beef, and pork intake, and physical exercise.
[d] Further adjusted for health check-ups for blood pressure and stomach and lung cancer screening.
[e] Overall incidence rate of colorectal cancer.
[f] Incidence rate of nonadvanced colorectal cancer.
[g] Incidence rate of advanced colorectal cancer.
[h] Additionally adjusted for use of hormone replacement therapy in women.

Table 4
Relative risk and 95% confidence interval for colorectal cancer screening and subsequent risk of colorectal cancer according to age groups in the JPHC Study[a]

	Unscreened	Screened
40–49 years (n = 20,541)		
Cancer deaths		
Person-years of follow-up	229597.3	40972.3
Colorectal cancer (n = 43)		
Number of deaths	40	3
RR (95% CI)[b]	1.00 (reference)	0.41 (0.13–1.32)
RR (95% CI)[c]	1.00 (reference)	0.47 (0.14–1.52)
RR (95% CI)[d]	1.00 (reference)	0.44 (0.13–1.46)
Cancer incidence		
Person-years of follow-up	218126.2	38572.3
Colorectal cancer[e] (n = 192)		
Number of cases	158	34
RR (95% CI)[b]	1.00 (reference)	1.22 (0.84–1.76)
RR (95% CI)[c]	1.00 (reference)	1.21 (0.83–1.77)
RR (95% CI)[d]	1.00 (reference)	1.18 (0.79–1.77)
Nonadvanced CRC[f] (n = 80)		
Number of cases	57	23
RR (95% CI)[b]	1.00 (reference)	2.24 (1.38–3.64)
RR (95% CI)[c]	1.00 (reference)	2.13 (1.29–3.53)
RR (95% CI)[d]	1.00 (reference)	1.95 (1.13–3.37)
Advanced CRC[g] (n = 99)		
Number of cases	90	9
RR (95% CI)[b]	1.00 (reference)	0.57 (0.29–1.14)
RR (95% CI)[c]	1.00 (reference)	0.60 (0.30–1.19)
RR (95% CI)[d]	1.00 (reference)	0.58(0.28–1.19)
50–59 years (n = 21,609)		
Cancer deaths		
Person-years of follow-up	226922.8	53966.3
Colorectal cancer (n = 89)		
Number of deaths	84	5
RR (95% CI)[b]	1.00 (reference)	0.25 (0.10–0.62)
RR (95% CI)[c]	1.00 (reference)	0.23 (0.08–0.62)
RR (95% CI)[d]	1.00 (reference)	0.27 (0.09–0.75)
Cancer incidence		
Person-years of follow-up	216276.9	51168.7
Colorectal cancer[e] (n = 405)		
Number of cases	344	61
RR (95% CI)[b]	1.00 (reference)	0.76 (0.58–0.99)
RR (95% CI)[c]	1.00 (reference)	0.70 (0.52–0.93)
RR (95% CI)[d]	1.00 (reference)	0.69 (0.51–0.94)
Nonadvanced CRC[f] (n = 180)		
Number of cases	142	38
RR (95% CI)[b]	1.00 (reference)	1.13 (0.79–1.62)
RR (95% CI)[c]	1.00 (reference)	1.10 (0.75–1.61)
RR (95% CI)[d]	1.00 (reference)	0.92 (0.62–1.37)
Advanced CRC[g] (n = 201)		
Number of cases	183	18
RR (95% CI)[b]	1.00 (reference)	0.42 (0.26–0.68)
RR (95% CI)[c]	1.00 (reference)	0.35 (0.20–0.60)
RR (95% CI)[d]	1.00 (reference)	0.39 (0.22–0.69)

[a] RR, relative risk; CI, confidence interval.
[b] Adjusted for sex and study area.
[c] Additionally adjusted for smoking status, alcohol intake, educational level, family history of colorectal cancer, body mass index, green-yellow vegetable, beef, and pork intake, and physical exercise.
[d] Further adjusted for health check-ups for blood pressure and stomach and lung cancer screening.
[e] Overall incidence rate of colorectal cancer.
[f] Incidence of nonadvanced colorectal cancer.
[g] Incidence rate of advanced colorectal cancer.

(RR = 0.23, 95% CI = 0.08–0.62), whereas no statistically significant decrease was seen in those aged 40–49 years (RR = 0.47, 95% CI = 0.14–1.52). Among subjects aged 50–59 years, a significant decrease in incidence of colorectal cancer was seen in incident cases of advanced colorectal cancer (RR = 0.35, 95% CI = 0.20–0.60), compared with no significant difference in the incidence of nonadvanced colorectal cancer. Moreover, the tendencies in different age groups did not change even after further adjustment for other screening histories or after the first 3 years of the follow-up period were excluded (data not shown). Moreover, when anatomical subsite was considered, additional analyses consistently showed a significant difference between the screened and unscreened groups in subjects aged 50–59 years, but no statistically significant difference in those aged 40–49 years. Among subjects aged 50–59 years, a significantly reduced risk of death from colon cancer, as well as from rectal cancer, was seen in screened versus unscreened subjects (RR = 0.29, 95% CI = 0.09–0.95; RR = 0.13, 95% CI = 0.02–0.97, respectively).

4. Discussion

The JPHC Study is an ongoing prospective population-based cohort study, designed to investigate the relation between lifestyle, diet and cancer, and has been conducted in Japan since 1990. The present results from the JPHC study represent the first prospective study of colorectal cancer screening in Japan.

With a follow-up period of 13 years, this study revealed a nearly 70% decrease in colorectal cancer mortality in screened versus unscreened subjects. The extent of mortality reduction was greater for colorectal cancer than for other causes. No statistically significant difference in colorectal cancer incidence was seen between the screened and unscreened groups. It is known that the only valid outcome variable in evaluating the effects of cancer screening is mortality rate. If incidence rate were measured as an alternative to mortality rate, it may increase with screening owing to artificial inflation by length bias or overdiagnosis bias [28]. Instead, when incidence rate of advanced colorectal cancer was considered as another outcome, a significant decrease was observed in the screened versus unscreened groups. The greater decrease in mortality than in incidence may be related to the improved survival, resulting from the higher possibility of early detection and early treatment afforded by colorectal cancer screening. In addition, the possibility of detecting other cancers may be

higher in screened than unscreened subjects owing to the greater accessibility of hospitals, a greater interest in health and so on.

In the age-stratified analyses, a significant reduction in colorectal cancer mortality of 77% was seen in screened subjects aged 50–59 years at baseline, compared with no statistically significant difference in those aged 40–49 years. Moreover, we observed a significant decrease in colorectal cancer incidence in those aged 50–59 years. This finding may suggest that there was a benefit of screening in subjects aged 50 or older.

Among previous randomized studies of FOBT, a Danish study [29] reported that screening was more effective in preventing death from colorectal cancer located proximal to the sigmoid colon than in that from more distal colorectal cancer (RR = 0.72, 95% CI = 0.55–0.95; RR = 0.92, 95% CI = 0.76–1.12, respectively), supporting a screening program using a combination of flexible sigmoidoscopy and FOBT. In contrast, the Nottingham study [6] reported mortality ratios of 0.87 (0.68–1.11) for cancer proximal to the sigmoid colon and 0.84 (0.70–1.00) for distal colorectal cancers, whereas no information is available from the Minnesota study [4,5]. In the present study, additional analyses by anatomical subsite showed a significant mortality reduction in the screened versus unscreened group among subjects aged 50–59 years at baseline, indicating that a significant reduction was seen in death from both colon and rectal cancer. This result is similar to those of previous case-control studies of immunochemical FOBT [9,30], and may suggest that screening using immunochemical FOBT is effective in reducing mortality in both colon and rectal cancer.

FOBT is the most cost-effective and comprehensively applicable screening method available, but its specificity and sensitivity are limited [1]. In Japan, immunochemical FOBT developed in 1983 was comparatively evaluated by a research committee organized by the Ministry of Health and Welfare. Results indicated the superiority of immunochemical method over previous FOBT in both sensitivity and specificity, and immunochemical FOBT has therefore been widely used as a screening test for colorectal cancer in Japan [9,10]. Although three landmark randomized studies reported significant reductions in colorectal cancer mortality in subjects screened using FOBT ranging from 15% to 33% [4–7,29], case-control studies of immunochemical FOBT showed a 40–76% reduced risk of death from colorectal cancer in screened subjects [9,10,12–14]. More significantly, however, selection bias could not be controlled in any of these case-control studies because no information on potential confounding factors was provided. Moreover, there has been no prospective study on the association between colorectal cancer screening using immunochemical FOBT and subsequent risk of colorectal cancer.

We therefore considered lifestyle factors and dietary habits that may have been associated with colorectal cancer in previous reports as potential confounding factors [20–27], with the expectation that statistical adjustment might be to some degree possible if information on associated variables were available. Additionally, to avoid the potential effects of past screenings, we repeated the analyses after excluding deaths and incident cases during the first 3 years of the follow-up period. These exclusions produced no substantial changes in trends, indicating that the effects of such bias were negligible. Moreover, to evaluate potential selection bias that may not have been controlled by adjustment for suspected or known associated confounding factors, death from causes other than colorectal cancer and incident cases from other causes excluding colorectal cancer were used as additional outcome variables. Therefore, we assessed the magnitude of potential selection bias by comparing the risk of death from other causes. Results showed that the extent of mortality reduction was greater for colorectal cancer than for other causes.

Another concern in this study was the validity of the exposure assessment. We determined the screened and unscreened subjects based on self-reports, and assumed that subjects who had undergone FOBT screening during the preceding 12 months were also screened during the follow-up period, whereas those who had not undergone preceding screening were not. Of course, this kind of misclassification may have resulted in attenuation of the true association. The 17% screening rate for a given 12-month period in this study was similar to national statistics, which indicate that 6 million inhabitants (17% of those aged 40 years or over) participated in colorectal cancer screenings organized by local governments. The subjects underwent follow-up survey in the fifth year after the baseline survey, and the data obtained were used to evaluate this assumption by comparing screening history between baseline and follow-up in the 35,175 subjects participating in both. Among those screened at baseline, the proportion who responded that they had also participated in colorectal cancer screening at follow-up was 60% (3819 of 6346). The respective proportion among those unscreened was 74% (21,229 of 28,829). Similar proportions were observed when the subjects were sex or age stratified. This finding suggests that recent screening participation can be a predictor of future participation. Further, the screened subjects seemed to have a greater awareness of health and health-promoting behavior than those unscreened.

Notwithstanding the known limitations of observational studies, the present study has the following strengths: it was a prospective population-based study with a 13-year follow-up period; information on screening experience was collected before the subsequent onset of cancer, eliminating the exposure recall bias that is inherent to case-control studies; study subjects were selected from the general population, and response rate to the baseline questionnaire was high while the proportion of losses to follow-up was negligible; and finally, adjustment was made for lifestyle factors and dietary habits that were shown to have been

possibly associated with colorectal cancer in previous reports [20–27].

In conclusion, we observed a significant reduction in colorectal cancer mortality in screened subjects. This association was observed in both sexes as well as in subjects aged 50–59 years. Although self-selection bias could not be fully controlled, these findings suggest that colorectal cancer screening using immunochemical FOBT may be associated with a reduction in mortality from colorectal cancer in the Japanese population. This study therefore supports recommendations for immunochemical FOBT as an approach to colorectal cancer prevention in the Japanese population.

Conflict of interest

None declared.

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Appendix A

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