Cancer Causes and Control 1995, 6, 14-22

Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan

Manami Inoue, Kazuo Tajima, Kaoru Hirose, Nobuyuki Hamajima, Toshiro Takezaki, Takashi Hirai, Tomoyuki Kato, and Yoshiyuki Ohno

(Received 27 June 1994; accepted in revised form 7 September 1994)

To investigate the subsite-specific risk factors for colorectal cancer, we conducted a case-control study, using a common questionnaire which inquired about general lifestyles over the past five years (1988-92), at the Aichi Cancer Center Hospital, Nagoya, Japan. This study compared 432 patients with histopathologically diagnosed colorectal cancer (94 proximal colon [cecum, ascending colon, transverse colon]; 137 distal colon [descending colon, sigmoid colon]; 201 rectum [rectosigmoid, rectum]); and 31,782 first-visit outpatient controls who were free from cancer. In both genders, habitual smoking selectively increased the risk for rectum cancer. Soft or loose feces increased the risk for all subsites of colorectal cancer, particularly in female rectum cancer (odds ratio [OR] = 4.5). Among female dietary habits, Japanese-style foods decreased the risk for distal colon cancer, but increased the risk for proximal colon cancer. These results suggested that the risk factors for colorectal cancer differ by subsite among such a low-risk population as the Japanese. It is suggested also that 'irritable bowel' (soft or loose feces) might be associated with distal subsites of colorectal cancer, independently or combined with habitual smoking. *Cancer Causes and Control* 1995, 6, 14-22.

Key words: Case-control study, colorectal cancer, Japan, risk factors, subsite.

Introduction

The incidence of and mortality from colorectal cancer show large international variations. In Japan, colorectal cancer is less common than in Western countries, but it has been increasing in recent years.[1-3] This increasing trend has been observed more markedly in colon cancer—more so in distal colon cancer—than in rectum cancer.[4] In migration studies, the incidence rate of colorectal cancer among Japanese immigrants in the United States was found to be close to or exceeding that among US Whites,[5] suggesting the strong relevance of environmental factors in the etiology of colorectal cancer.

The difference in the etiology of colorectal cancer by subsite has been determined in previous studies,[6,7] which suggested that environmental factors are related more strongly to distal colon cancer and host-specific factors to proximal colon cancer. On the other hand, risk factors for rectal cancer were reported to be different from that for colon cancer, and similar to that for gastric cancer in Japan.[8] Since separate analysis is

Drs Inoue and Tajima, Ms Hirose, and Drs Hamajima and Takezaki are with the Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya, Japan. Authors are also affiliated with the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan (Drs Hirai and Kato), and the Department of Preventive Medicine, Nagoya University School of Medicine, Nagoya, Japan (Drs Inoue and Ohno). Address correspondence to Dr Inoue, Division of Epidemiology, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya, Japan, 464. *This study was funded in part by a Grant-in-Aid for Cancer Research (4-2) and the Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health and Welfare, Japan.*

believed to be important when assessing risk factors for colorectal cancer, several subsite analyses[9-12] have been conducted, but the results were generally inconsistent. Moreover, subsite analysis within the colon in Japanese as well as other Asian populations rarely has been conducted. When considering an increasing trend of distal colon cancer according to the changing life-styles over time,[4] particularly after World War II in Japan, we should clarify subsite-specific risk factors for colorectal cancer. For these reasons, it is necessary to evaluate risk factors separately for each subsite of colorectal cancers.

To investigate the subsite-specific risk factors for colorectal cancer in the low-risk Japanese population, we conducted a comparative case-control study of three subsites of colorectal cancer, *i.e.*, proximal colon, distal colon, and rectum. In this study, we focused mainly on environmental factors, *e.g.*, habitual smoking and drinking, physical exercise, bowel habit, and dietary habits. Reproductive factors and other host-related factors, which also are believed to be risk factors for some subsites of colorectal cancer, will be discussed elsewhere.

Materials and methods

Since 1988, information on lifestyles has been collected routinely by means of a self-administered questionnaire from all first-visit outpatients at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan. Each outpatient is asked about his or her general lifestyle when healthy or before current symptoms developed. Details of the questionnaire and data collection procedures are described elsewhere.[13,14] The present study was based on data collected from January 1988 to December 1992.

Among all first-visit outpatients in this period ($n = 40{,}420$), the questionnaire was administered to 37,882 (93.7 percent). The remaining 2,538 (6.3 percent) were excluded because of: young age (under 18 years old) (466 patients, 1.2 percent); absence of the interviewer (1,552 patients, 3.8 percent); or because someone other than the patient attended the consultation (520 patients, 1.3 percent). Of the 37,882 outpatients, 36,944 (97.5 percent) provided an adequate response to the questionnaire. Among them, 5,162 cancer patients (14.0 percent) were identified by the hospital cancer-registry system.

In the present study, controls comprised 31,782 non-cancer outpatients (23,161 females and 8,621 males) who had their first hospital-visit during this period and were confirmed to be cancer-free by diagnostic procedure at ACCH, and had no past history of cancer. To assess the proportional distribution of clinical diagnosis among non-cancer outpatients, we randomly sampled 10 percent of those outpatients ($n = 2{,}997$) and confirmed their final diagnosis by medical records (Table 1). Forty-four percent were found to have no abnormal findings by examinations; 13 percent had benign tumors or non-neoplastic polyps; and the other 35 percent were confirmed to have benign and nonspecific disease.

Table 1. Proportional distribution of diagnosis among non-cancer outpatients[a] in Aichi Cancer Center Hospital (1988-92)

Diagnosis	(%)		
Disease free	44.3		
Benign tumor, non-neoplastic polyp	13.1		
Colonic polyp		2.7	
Breast fibroadenoma		2.1	
Gastric polyp		2.0	
Cystic disease	3.4		
Breast cyst		1.7	
Other diseases	39.2		
Breast[b]		7.5	
Upper gastro-intestinal tract		4.1	
(Atrophic gastritis)			(2.2)
(Gastric ulcer)			(1.6)
Reproductive system		4.1	
(Myoma uteri)			(1.7)
(Vaginitis)			(1.2)
Hepatobiliary system and pancreas		1.5	
Respiratory system		1.2	
Miscellaneous		20.8	
Total	100.0		

[a]Randomly selected 10% of non-cancer outpatients ($n = 2{,}997$/31,782).
[b]All cases are mastitis.

All patients with incident colorectal cancer received surgical treatment, and their diagnoses were confirmed with subsite-specific information on the basis of both clinical and histopathologic examination at ACCH between January 1988 and December 1992. Of 467 eligible patients, 35 were excluded because of insufficient response to the questionnaire. A total of 432 colorectal cancer patients (175 females and 257 males) were recruited as cases in the present study.

By means of surgical observation, the patients were divided into groups by anatomic subsite of colorectum according to the primary lesion, *i.e.*, cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, and rectum. Determination of the anatomic subsites was based on the *General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus, 4th Edition.*[15] For the subsite analysis in the present study, these anatomic subsites were grouped further into three categories: proximal colon (cecum, ascending colon, transverse colon); distal

colon (descending colon, sigmoid colon); and rectum (rectosigmoid, rectum). Consequently, the 432 cases consisted of 94 patients with proximal colon cancer (43 females and 51 males), 137 with distal colon cancer (62 females and 75 males), and 201 with rectal cancer (70 females and 131 males).

Plausible risk or protective factors in colorectal cancer were selected from the lifestyle questionnaire based on the previous study.[8] These included: habitual drinking and smoking; physical exercise; softness of feces; dietary practice (type of breakfast, preference of salty or greasy food, size of meal); intake frequency of Japanese-style foods (rice, soybean paste [miso] soup, bean curd [tofu], pickled vegetables, salted or dried fish, cooked or raw fish); intake frequency of vegetables and fruit (fresh vegetables, fruit, green vegetables, carrot, pumpkin, cabbage, lettuce, potato); and intake frequency of meat and Western-style foods (egg, chicken, beef, pork, ham and sausage, milk). These items were dichotomized individually by habitual practice or intake frequency.

All analyses were conducted separately by gender and subsite of colorectal cancer. Odds ratios (OR) and their 95 percent confidence intervals (CI) were estimated using unconditional logistic regression models, adjusting for age (continuous). To control the effect of confounding variables, when evaluating an association between each lifestyle and colorectal cancer subsites, we carried out multivariate logistic regression, including age and all significant variables found in each univariate analysis (*e.g.*, habitual smoking, softness of feces, type of breakfast, preference of salty food, intake frequency of rice, bean curd, pickled vegetables, fruit, carrot, ham and sausage, and milk for females; and habitual smoking, softness of feces, preference of salty food, intake frequency of bean curd, green vegetables, egg, and chicken for males). In this analysis, we confirmed in advance that these items were not correlated with each other. Procedure LOGISTIC from SAS[16] was used to perform the calculation.

Results

The age of diagnosis of colorectal cancer ranged from 24 to 88 years old in female cases and 24 to 86 in male cases. Average age of the cases was 58.6 years in females (proximal colon: 59.5; distal colon: 56.8; rectum: 57.1) and 60.6 years in males (proximal colon: 61.0; distal colon: 63.6; rectum: 60.6). Average age of the controls was 45.7 years in females and 50.3 years in males. In all subsites, there were sufficient numbers of cases in all age strata to do age-adjustment.

Table 2 shows the ORs of habitual drinking and smoking, physical exercise, and softness of feces. Habitual smoking (current and ex-smoking) increased the risk for rectal cancer in females (OR = 1.7, CI = 1.0-3.1) and in males (OR = 1.9, CI = 1.1-3.2). Soft feces increased the risk for all subsites in females (proximal colon: OR = 2.0, CI = 1.0-3.9; distal colon: OR = 2.0, CI = 1.1-3.6; rectum: OR = 4.5, CI = 2.8-7.2) and in males (proximal colon: OR = 2.0, CI = 1.1-3.5; distal colon: OR = 1.6, CI = 1.0-2.6; rectum: OR = 2.4, CI = 1.7-3.3), ORs being higher for the rectum and in females. Habitual drinking (current and ex-drinking) was likely to decrease the risk for both colon cancer subsites and increase the risk for rectum

Table 2. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) of selected lifestyles for colorectal cancer by subsite

Variable	% of exposed subjects among controls	Proximal colon ($n = 42$)		Distal colon ($n = 61$)		Rectum ($n = 70$)	
		OR	(CI)	OR	(CI)	OR	(CI)
Females							
Habitual drinking	28.1	0.8	(0.3-1.8)	0.8	(0.4-1.5)	1.3	(0.7-2.2)
Habitual smoking	16.2	0.9	(0.4-2.4)	1.1	(0.6-2.3)	1.7	(1.0-3.1)
Physical exercise	11.9	0.5	(0.2-1.5)	1.0	(0.5-2.0)	0.7	(0.3-1.4)
Softness of feces	14.4	2.0	(1.0-3.9)	2.0	(1.1-3.6)	4.5	(2.8-7.2)
Males							
Habitual drinking	70.8	1.3	(0.7-2.5)	1.1	(0.7-1.9)	1.1	(0.7-1.6)
Habitual smoking	78.0	0.7	(0.4-1.4)	1.0	(0.6-1.7)	1.9	(1.1-3.2)
Physical exercise	15.8	0.7	(0.4-1.5)	0.7	(0.4-1.3)	0.8	(0.5-1.3)
Softness of feces	33.0	2.0	(1.1-3.5)	1.6	(1.0-2.6)	2.4	(1.7-3.3)

Contrast: Habitual drinking: drinker (current and ex-) *cf* nondrinker; Habitual smoking: smoker (current and ex-) *cf* nonsmoker; Physical exercise: more than 3-4 times/month *cf* less; Softness of feces: soft or loose *cf* moderate or hard.

Table 3. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) of selected dietary practice and food items for colorectal cancer by subsite (females)

	% of exposed subjects among controls	Proximal colon ($n = 42$)		Distal colon ($n = 61$)		Rectum ($n = 70$)	
		OR	(CI)	OR	(CI)	OR	(CI)
Dietary practice							
Type of breakfast	31.1	1.8	(1.0-3.3)	1.4	(0.8-2.4)	0.8	(0.5-1.4)
Salty food	61.3	0.6	(0.3-1.0)	0.9	(0.5-1.5)	0.7	(0.5-1.2)
Greasy food	48.7	1.0	(0.5-1.8)	0.9	(0.5-1.5)	1.4	(0.9-2.2)
Size of meal	49.4	1.6	(0.9-3.0)	0.7	(0.4-1.2)	0.9	(0.6-1.5)
Japanese-style foods							
Rice	41.6	1.1	(0.6-2.1)	0.6	(0.3-1.0)	1.0	(0.6-1.6)
Soybean paste soup	59.4	0.8	(0.4-1.4)	0.8	(0.5-1.3)	1.1	(0.7-1.8)
Bean curd	46.3	1.3	(0.7-2.4)	0.6	(0.4-1.0)	0.9	(0.6-1.5)
Pickled vegetables	13.7	1.4	(0.7-2.9)	0.6	(0.3-1.2)	2.1	(1.2-3.5)
Salted or dried fish	9.2	1.2	(0.5-2.8)	0.7	(0.3-1.7)	1.4	(0.8-2.7)
Cooked or raw fish	32.2	1.4	(0.8-2.5)	1.0	(0.6-1.7)	1.4	(0.9-2.2)
Vegetables and fruit							
Fresh vegetables	39.1	0.9	(0.5-1.6)	0.8	(0.5-1.4)	1.2	(0.7-1.9)
Fruit	46.7	1.3	(0.7-2.4)	0.4	(0.3-0.8)	0.9	(0.6-1.5)
Green vegetables	56.5	0.8	(0.5-1.6)	0.9	(0.6-1.6)	1.0	(0.6-1.6)
Carrots	48.8	0.6	(0.3-1.1)	1.2	(0.7-1.9)	0.7	(0.4-1.1)
Pumpkin	13.1	1.7	(0.9-3.4)	0.6	(0.3-1.3)	0.9	(0.5-1.7)
Cabbage	45.9	0.9	(0.5-1.6)	1.2	(0.7-2.0)	1.1	(0.7-1.7)
Lettuce	38.8	1.6	(0.9-3.0)	1.0	(0.6-1.7)	1.1	(0.7-1.8)
Potatoes	38.5	1.1	(0.6-2.1)	1.0	(0.6-1.7)	1.0	(0.6-1.7)
Meats and Western-style foods							
Eggs	70.9	1.0	(0.5-1.9)	1.0	(0.6-1.7)	0.8	(0.5-1.4)
Chicken	22.7	1.6	(0.9-3.0)	1.3	(0.7-2.2)	1.0	(0.6-1.7)
Beef	11.0	1.5	(0.6-3.5)	1.3	(0.6-2.8)	0.8	(0.4-1.9)
Pork	17.5	1.8	(0.8-3.8)	0.7	(0.3-1.5)	0.9	(0.4-1.8)
Ham and sausage	15.1	1.6	(0.7-3.6)	0.8	(0.4-1.9)	1.9	(1.1-3.5)
Milk	45.2	0.7	(0.4-1.3)	0.9	(0.6-1.6)	0.6	(0.3-0.9)

Contrast: Type of breakfast: Western *cf* Japanese; Salty food, greasy food: liked *cf* disliked; Size of meal: large *cf* small; Soybean paste soup, fresh vegetables, fruit, milk: everyday *cf* less; Rice: more than 3-4 bowls/day *cf* less; Else: more than 3-4 times/week *cf* less.

cancer in females. In males, the risk appeared to be increased solely at the proximal colon. Physical exercise tended to decrease the risk for all subsites in both genders except female distal-colon cancer.

In females, eating a Western-style breakfast increased the risk for both proximal colon cancer (OR = 1.8, CI = 1.0-3.3) and distal colon cancer, and decreased the risk for rectal cancer (Table 3). Preference of salty food decreased the risk for all subsites, particularly for proximal colon cancer (OR = 0.6, CI = 0.3-1.0). Consumption of Japanese-style foods generally decreased the risk for distal colon cancer, while increasing the risk for proximal colon and rectal cancer. The decreased risk of distal colon cancer by a large intake of rice (OR = 0.6, CI = 0.3-1.0) and the increased risk by pickled vegetable intake were statistically significant (OR = 2.1, CI = 1.2-3.5). For intake of vegetables and fruit, only fruit decreased the risk for distal colon cancer (OR = 0.4, CI = 0.3-0.8). In consumption of meats and Western-style foods, egg was not linked to the risk for any subsite of colon cancer, and milk tended to decrease the risk for all subsites. Chicken, beef, and pork increased proximal colon cancer risk, but reduced rectum cancer risk. Intake of ham and sausage increased rectal cancer risk (OR = 1.9, CI = 1.1-3.5).

In males, risk modifications were inconsistent compared with those in females (Table 4). For example, salty food increased the risk for proximal colon cancer (OR = 2.4, CI = 1.5-5.1) and bean curd increased the risk for distal colon cancer (OR = 1.7, CI = 1.0-2.6). Inconsistency also was observed in vegetables and fruit intake; for instance, more frequent intake of fruit and green vegetables increased the risk for distal colon cancer (fruit: OR = 1.4, CI = 0.9-2.3; green vegetables: OR = 1.7, CI = 1.0-2.7), and carrots

increased the risk for proximal colon cancer. Consumption of eggs increased proximal colon cancer risk selectively (OR = 2.0, CI = 1.0-4.0). Milk reduced the risk for both proximal and distal colon cancer, but not for rectal cancer. Ham and sausage increased the risk of cancer at all subsites, however, chicken and pork decreased it.

The ORs of multivariate analysis were not very different from those obtained from univariate analyses. The risk trend of dietary habits is presented in Table 5 to summarize the relation of dietary habits to colon cancer.

Discussion

An important methodologic issue may be bias derived from discrepant characteristics between the general population and the hospital-based controls.

In Japan, outpatients, in general, visit hospitals when they have symptoms, and the numbers of outpatients who visit general clinics has been decreasing and those who visit hospitals has been increasing in the past 10 to 15 years.[17] This situation is different from that in other countries, where people visit local general clinics first, and then a hospital functions as a secondary facility for further medical treatment. Over the last 30 years, ACCH has been regarded as a cancer hospital, but has not functioned as a secondary hospital for cancer, and most new outpatients visited this hospital independently, rather than by doctors' referrals. Therefore, patients with incident cancer comprised only 14 percent of all new outpatients. Among non-cancer outpatients, more than 80 percent were confirmed to be free from any specific diseases. We are, therefore, at an advantage in having non-cancer outpatients as controls, most of whom were not hospitalized and

Table 4. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) of selected dietary practice and food items for colorectal cancer by subsite (males)

	% of exposed subjects among controls	Proximal colon (n = 50)		Distal colon (n = 75)		Rectum (n = 131)	
		OR	(CI)	OR	(CI)	OR	(CI)
Dietary practice							
Type of breakfast	26.2	0.9	(0.5-1.8)	1.4	(0.8-2.2)	1.0	(0.7-1.5)
Salty food	74.5	2.4	(1.1-5.1)	1.1	(0.7-1.9)	0.9	(0.6-1.4)
Greasy food	61.1	1.1	(0.6-1.9)	1.0	(0.6-1.6)	1.3	(0.9-1.9)
Size of meal	47.5	1.5	(0.9-2.7)	1.1	(0.7-1.8)	1.2	(0.8-1.7)
Japanese-style foods							
Rice	61.2	0.9	(0.5-1.6)	0.9	(0.5-1.4)	1.1	(0.8-1.6)
Soybean paste soup	65.9	1.2	(0.6-2.2)	0.7	(0.4-1.1)	0.8	(0.6-1.2)
Bean curd	38.0	0.9	(0.5-1.6)	1.7	(1.0-2.6)	1.2	(0.8-1.7)
Pickled vegetables	16.7	0.9	(0.5-1.8)	0.7	(0.4-1.4)	1.1	(0.7-1.7)
Salted or dried fish	10.3	1.1	(0.5-2.5)	1.1	(0.5-2.1)	1.5	(0.9-2.3)
Cooked or raw fish	33.5	0.9	(0.5-1.7)	1.2	(0.8-1.9)	1.0	(0.7-1.4)
Vegetables and fruit							
Fresh vegetables	37.1	1.1	(0.6-1.9)	0.9	(0.6-1.5)	1.0	(0.7-1.4)
Fruit	30.3	1.0	(0.6-1.9)	1.4	(0.9-2.3)	0.8	(0.6-1.2)
Green vegetables	39.5	1.4	(0.8-2.4)	1.7	(1.0-2.6)	0.9	(0.6-1.3)
Carrots	23.2	1.6	(0.9-2.8)	1.1	(0.6-1.8)	1.0	(0.7-1.5)
Pumpkin	6.7	0.6	(0.2-1.9)	1.3	(0.6-2.5)	1.2	(0.7-2.2)
Cabbage	37.3	0.7	(0.4-1.3)	1.1	(0.7-1.8)	1.2	(0.8-1.7)
Lettuce	26.9	1.2	(0.6-2.1)	1.2	(0.7-2.0)	1.2	(0.8-1.8)
Potatoes	18.9	0.6	(0.3-1.3)	1.3	(0.8-2.2)	1.0	(0.7-1.5)
Meats and Western-style foods							
Eggs	63.8	2.0	(1.0-4.0)	1.2	(0.7-1.9)	1.0	(0.7-1.4)
Chicken	16.1	0.6	(0.3-1.4)	0.8	(0.4-1.5)	0.6	(0.3-1.0)
Beef	10.7	1.3	(0.6-3.1)	1.1	(0.5-2.3)	0.7	(0.4-1.4)
Pork	11.0	0.4	(0.1-1.8)	0.8	(0.3-2.0)	0.7	(0.3-1.4)
Ham and Sausage	12.7	1.4	(0.6-3.1)	1.6	(0.8-3.0)	1.3	(0.8-2.2)
Milk	38.4	0.7	(0.4-1.3)	0.9	(0.6-1.5)	1.3	(0.9-1.8)

Contrast: Type of breakfast: Western *cf* Japanese; Salty food, greasy food: liked *cf* disliked; Size of meal: large *cf* small; Soybean paste soup, fresh vegetables, fruit, milk: everyday *cf* less; Rice: more than 3-4 bowls/day *cf* less; Else: more than 3-4 times/week *cf* less.

Table 5. Summary table of risk trend of dietary habits for colorectal cancers by subsite

	Subsite					
	Proximal colon		Distal colon		Rectum	
	Female	Male	Female	Male	Female	Male
Western-style breakfast	**↑**	→	↑	↑	↓	→
Japanese-style foods	→	→	**↓**	?	**↑**	→
Fruit	→	→	**↓**	↑	→	↓
Vegetables	→	?	→	**↑**	→	→
Meat	↑	?	→	→	→	**↓**

↑, increase; →, no change; ↓, decrease; ?, undetermined.
Bold arrow indicates statistically significant level.

were disease-free. Further, we conducted the questionnaire study before the patients' diseases were identified, and thus were able to keep recall bias between cases and controls to as low a level as possible.

To ascertain the discrepant features of general lifestyles in outpatients (*i.e.*, to understand the characteristics of our control group), one suitable indicator may be smoking prevalence. Smoking prevalence in the general population in Japan is 15.9 percent among females (current smokers: 10.8 percent, ex-smokers: 5.1 percent) and 79.0 percent among males (current smokers: 59.3 percent, ex-smokers: 19.7 percent).[18] The smoking prevalence of our control group was 16.2 percent among females (current smokers: 12.1 percent, ex-smokers: 4.1 percent) and 78.0 percent among males (current smokers: 47.2 percent, ex-smokers: 30.8 percent). These figures were not very discrepant with each other in both genders, although a slightly higher rate of ex-smokers was noted in the male control group. Another indicator may be socioeconomic status. We, however, did not include questions on socioeconomic status in our questionnaire, because Japanese are rather reluctant to answer such questions; it generally is acknowledged that the majority of Japanese are socioeconomically middle-class. When comparing outpatients with the general population, we found that the lifestyles of most outpatients who visited ACCH for the first time were not very different from those of community residents (unpublished data). Consequently, we judged that it is feasible to use these non-cancer outpatients as a reference group in our case-control study.

The importance of self-selection bias in our controls is not emphasized in the present study because our purpose was to clarify the difference and/or similarity of risk factors of colorectal cancer by subsite, compared with the common controls. Our previous study,[19] which analyzed the variation of ORs by matched analyses using the same outpatient controls, indicated that the ORs based on a large number of controls gave much steadier estimates than those obtained by matched analyses. Therefore, we used all non-cancer individuals as pooled controls, instead of matched sampling in the present case-control study.

When evaluating risk factors for each subsite of colorectal cancer, definition and reliability of subdivision are the principal issues. Some studies[9,11] classified transverse colon into distal colon, and another study[20] classified it into proximal colon. Anatomically, most of the transverse colon gets its blood supply from the middle colic artery, which is the branch of the superior mesenteric artery that also feeds the cecum and ascending colon through the right colic artery and ileocolic artery. In the present study, therefore, we classified transverse colon into proximal colon. We also classified the rectosigmoid subdivision into a part of the rectum because of the similar physiologic function and gender distribution between them (female/male ratio: sigmoid = 0.87, rectosigmoid = 0.66, rectum = 0.50). The rectosigmoid cases also could be classified into sigmoid cancer depending on the similarity or difference in the etiology. It is preferable, therefore, to conduct a comparative study among all anatomic subsites of colorectal cancer to resolve this issue, however we had too few cases in each subdivision.

In the present study, habitual smoking increased the risk of rectal cancer selectively in both genders. Thus far, an association of habitual smoking with colorectal cancer has been considered to be weak or negative in previous studies.[21,22] It is suggested that the known carcinogenic agents in cigarette smoke are unlikely to have a direct selective effect on most subsites of colorectum. Further, it has been suggested[23-25] that chronic nicotine exposure from habitual smoking effects a low-estrogen condition, and may reduce the risk of ovary, thyroid, and breast cancers. It also is

known that nicotine stimulates bowel movement and shortens the exposure time of feces to the intestinal wall, which may reduce the risk of colorectal cancer. If some subsite of colorectal cancer is related to estrogen levels, habitual smoking may reduce the risk of cancer of that subsite. Indeed, the risk of cancer in smokers decreased in both proximal and distal colon in the present study. It is suggested that, in the least, the risk of smoking is different between rectal cancer and proximal and distal colon cancer. Recent reports suggested a positive association of habitual smoking with colorectal adenoma and cancer after allowing a long induction period[26,27] although subsite-specific risk for colorectal cancer was not determined.

Immunologically, the activity of the natural killer (NK) cell is reduced by habitual smoking.[28,29] Experimental study suggests that NK cells play an important role in the defense mechanism against tumor growth.[30] Thus, the effects of habitual smoking may play an important role in cancer progression by lowering NK cell activity, while the relation to subsite-specificity is still unclear.

Soft or loose feces increased the risk of colorectal cancer in all subsites, and the risk increased as subsite became distal. The relation between bowel habit and colorectal cancer seldom has been discussed. An epidemiologic study of the Japanese population[31] showed the association of both soft and hard feces and colorectal cancer. Physiologic function is different among the three colorectal subsites. In the proximal colon, the feces are in liquid or fluid form and are moved by peristalsis; therefore, it is suggested that soft or loose feces does not act as an irritable substance in the proximal part of the colon. But if it goes to the distal part of colorectum, the feces become more solid and transit time is longer.[10] Soft feces then may become more irritable in the distal part of colorectum. It is hypothesized that soft feces stimulate the intestinal mucosa in the distal part and promote carcinogenesis, especially in the rectum.

In experimental studies, higher levels of prostaglandin E2 (PGE2) in the diarrheal state have been reported, which have caused more marked excitation in the distal region of the gastrointestinal tract.[32] Further, increased PGE2 level was suggested to be associated with the large bowel carcinogenesis.[33] This association also was supported by the studies which demonstrated the inhibition of colon carcinogenesis by such nonsteroidal anti-inflammatory drugs as indomethacin and aspirin, which are inhibitors of prostaglandin synthesis.[34] Therefore, it is suggested that frequent irritation to the intestinal mucosa promotes carcinogenesis with the high level of PGE2 and it may occur more readily under the condition of an immunologically less-active state among habitual smokers. However, if the interval between onset of bowel symptoms and diagnosis of cancer is very long, we cannot deny the possibility that soft or loose feces and also constipation are a result of the disease. Further epidemiologic study, therefore, is needed to support this hypothesis, and basic studies would clarify the mechanism of carcinogenesis in the large bowel.

In the present study, we could not obtain consistent findings for dietary risk factors between women and men, although they were claimed as risk or protective factors in Western populations.[35,36] Response to the questionnaire, especially regarding dietary habits, might be more precise and reliable in females than in males, because, in general, females in Japan prepare their own meals and are more conscious of diet. From the present study, the consistency within the same food group was more marked in females than in males.

There is a hypothesis that the risk factors related to bile metabolism, dietary fat, and cholesterol, for example, are related more directly to proximal colon cancer. Higher intake of these foods promotes the production and secretion of bile acids, which increases the concentration of secondary bile acids in the colorectum, and consequently promotes carcinogenesis of proximal colon cancer.[7] In Western countries, eggs are one of the important contributors of cholesterol, with a powerful induction of gallbladder contraction and release of bile acids into the colon.[12] Egg consumption was reported as a positive risk factor for colon cancer, conferring higher risk in females than in males.[9,12] In our study, however, intake of eggs increased the risk for proximal colon cancer in males, but not in females. Intake of chicken, beef, and pork was the index for animal fat. In females, these food items increased the risk for proximal colon cancer, but the risk modification by these foods was inconsistent in males.

Consumption of Japanese-style foods increased the risk for rectal cancer, and decreased the risk for distal colon cancer, especially in females (Table 3). This supports a hypothesis that the risk factors differ between colon and rectum. In males, on the other hand, the results were inconsistent. For example, consumption of bean curd—a traditional Japanese food—which is expected to be a protective factor, appeared to reduce the risk in females, but increased the risk for distal colon cancer in males. There is no clear explanation for this discrepant modification. Western-type breakfast was not associated with rectal cancer risk in either gender, but increased the risk for distal colon cancer in males and both proximal and distal colon cancer in females. This finding is not contradictory to the time trend of colorectal cancer incidence in Japan.

We must be cautious in interpreting the findings that colorectal cancer and Japanese dietary habits are interrelated, especially in the light of the Western-style dietary habits. In a usual Japanese diet, very few people would eat at least one animal-meat item everyday, because most main dishes usually alternate between meat and fish on a daily basis. In Japan, amount of meat intake is low compared with that in Western countries,[37] therefore, it may be difficult to determine a consistent positive and/or negative relation between meat intake and colorectal cancer. A similar argument could be made that vegetables and fruit reduced the risk for distal colon or rectal cancer in females, while the results were inconsistent in males. Unexpectedly in males, fruit, green vegetables, and carrot elevated the risk site-specifically, *i.e.*, vegetables and fruit are known as protective factors for many sites of cancers by recent studies of β-carotene, etc.[38,39]

This inconsistency may be due to inter-country variation of general food-styles between Asian and Western people. Compared with the people in the West, Asian people, including Japanese, are principally vegetarian. The percent contribution of fat to total energy intake is 20 to 25 percent among Japanese,[40] which was much lower than that in the West. Along with the dramatic economic development after World War II in Japan, nutritional status has been changed gradually, as well, by availability of animal meat and fat.[37] As a consequence, the Japanese diet is more Western-style (but not to the degree of present style in the West) and is richer in variety and better balanced in nutrients than before. Such dietary change has spread throughout Japan, and recent variations in Japanese dietary practices would become smaller in quality and quantity. Therefore, it becomes more difficult to identify dietary risk factors for specific epidemiologically, *i.e.*, 'good' or 'bad' dietary habits among Japanese. In the light of these dietary changes in Japan, and international differences in dietary practices, it may not be appropriate to apply the dietary findings obtained from the study of Western populations to the Japanese.

In summary, we found that habitual smoking had a positive effect on rectal cancer selectively, and soft or loose feces play an important role in the progression of colorectal cancer. In females, a positive relationship between the Western-style breakfast and distal colon cancer was observed. There was also a positive relationship between the intake of Japanese-style foods and rectal cancer, an inverse relationship between Japanese-style foods and distal colon cancer, and a protective effect of fruit and vegetables—although this risk modification was rather inconsistent in males. In short, further epidemiologic studies, particularly in populations at low-risk of colorectal cancer such as Japanese and other Asian populations, are necessary to interpret the present findings properly, when taking obvious international variations of dietary practices into account.

Acknowledgements—The authors are grateful to Mss Hiroko Fujikura, Yukiko Yamauchi, Etsuko Nakamura, and Michiyo Takasaki for their data collection and preparation, and Mr Erick C Ubels for his linguistic support.

References

1. Waterhouse J, Muir CS. Shanmugaratnam J, Powell J, eds. *Cancer Incidence in Five Continents, Vol. IV.* Lyon, France: International Agency for Research on Cancer, 1982; IARC Sci. Pub. No. 42: 710-3.
2. Muir CS, Waterhouse J, Mack T, Powell J, Whelan SL, eds. *Cancer Incidence in Five Continents, Vol. V.* Lyon, France: International Agency for Research on Cancer, 1987; IARC Sci. Pub. No. 88: 852-5.
3. Parkin DM, Muir CS, Whelan SL, Gao YT, Feray J, Powell J, eds. *Cancer Incidence in Five Continents, Vol. VI.* Lyon, France: International Agency for Research on Cancer, 1992; IARC Sci. Pub. No. 120: 924-9.
4. Tajima K, Hirose K, Nakagawa N, Kuroishi T, Tominaga S. Urban-rural difference in the trend of colo-rectal cancer mortality with special reference to the subsites of colon cancer in Japan. *Jpn J Cancer Res* 1985; **76:** 717-28.
5. Shimizu H, Mack TM, Ross RK, Henderson BE. Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. *JNCI* 1987; **78:** 223-8.
6. Vernick LJ, Kuller LH. A case-control study of cholecystectomy and right-side colon cancer. *Am J Epidemiol* 1982; **116:** 86-101.
7. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolism profiles that selectively increase the risk of proximal colon cancer. *JNCI* 1985; **75:** 185-91.
8. Tajima K, Tominaga S. Dietary habits and gastrointenstinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985; **76:** 705-16.
9. Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer*, 1988; **42:** 167-75.
10. Peters RK, Garabrant DH, Yu MC, Mack TM. A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. *Cancer Res* 1989; **49:** 5459-68.
11. Steinmetz KA, Potter JD. Food-group consumption and colon cancer in Adelaide case-control study. I. Vegetables and fruit. *Int J Cancer* 1993; **53:** 711-9.
12. Steinmetz KA, Potter JD. Food-group consumption and colon cancer in Adelaide case-control study. II. Meat, poultry, seafood, dairy foods and eggs. *Int J Cancer* 1993; **53:** 720-7.
13. Yoo KY, Tajima K, Kuroishi T, *et al.* Independent protective effect of lactation against breast cancer: a case-control study in Japan. *Am J Epidemiol* 1992; **135:** 726-33.

14. Inoue M, Tajima K, Hirose K, Kuroishi T, Gao CM, Kito T. Life-style and subsite of gastric cancer—joint effect of smoking and drinking habit. *Int J Cancer* 1994; **56:** 494-9.
15. Japanese Research Society for Cancer of Colon and Rectum. *The General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus, 4th Edition.* Kanehara-Shuppan, Japan: Japanese Research Society for Cancer of Colon and Rectum, 1985.
16. SAS Institute Inc. *SAS/STAT User's Guide*, Version 6. Cary, NC (USA): SAS Institute Inc., 1990.
17. *Patients and Medical Institutions in Japan—Graphical Review of Health Statistics—1992*. Tokyo, Japan: Health and Welfare Statistics Association, 1992.
18. *The Report of Nationwide Survey on Health Promotion in 1990*. Tokyo, Japan: Japan Health Promotion and Fitness Foundation, 1990.
19. Hamajima N, Hirose K, Inoue M, Takezaki T, Kuroishi T, Tajima K. Case-control studies: matched controls or all available controls? *J Clin Epidemiol* 1994; **47:** 971-5.
20. West DW, Slattery ML, Robinson LM, *et al.* Dietary intake and colon cancer: sex- and anatomic site-specific associations. *Am J Epidemiol* 1989; **130:** 883-94.
21. Haenszel W, Locke FB, Segi M. A case-control study of large bowel cancer in Japan. *JNCI* 1980; **64:** 17-22.
22. Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the etiology of cancers of the digestive tract. *Int J Cancer* 1991; **49:** 381-6.
23. Baron JA. Smoking and estrogen-related disease. *Am J Epidemiol* 1984; **119:** 9-22.
24. O'Connell DL, Hulka BS, Chambless LE, Wilkinson WE, Deubner DC. Cigarette smoking, alcohol consumption, and breast cancer risk. *JNCI* 1987; **78:** 229-34.
25. Sandler RS, Sandler DP, Comstock GW, Helsing KJ, Shore DL. Cigarette smoking and the risk of colorectal cancer in women. *JNCI* 1988; **80:** 1329-33.
26. Giovannucci E, Rimm EB, Stampfer MJ, *et al.* A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. *JNCI* 1994; **86:** 183-91.
27. Giovannucci E, Colditz GA, Stampfer MJ, *et al.* A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *JNCI* 1994; **86:** 192-9.
28. Kusaka Y, Kondou H, Morimoto K. Healthy lifestyles are associated with higher natural killer cell activity. *Prev Med* 1992; **21:** 602-15.
29. Nakachi K, Imai K. Environmental and physiological influences on human natural killer cell activity in relation to good health practices. *Jpn J Cancer Res* 1992; **83:** 798-805.
30. Trinchieri G. Biology of natural killer cells. In: Dixon FJ, ed. *Advances in Immunology*. San Diego, CA (USA) Academic Press, 1989: 187-376.
31. Kato I, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S. Case-control study of bowel habits and colorectal adenoma and cancer. *J Epidemiol* 1993; **3:** 1-5.
32. Burakoff R, Percy WH. Studies in vivo and in vitro on effects of PGE2 on colonic motility in rabbits. *Am J Physiol* 1992; **262:** G23-9.
33. Reddy BS, Rao CV, Rivenson A, Kelloff G. Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F334 rats. *Carcinogenesis* 1993; **14:** 1493-7.
34. Yamaguchi A, Ishida T, Nishimura G, Katoh M, Miyazaki I. Investigation of colonic prostaglandins in carcinogenesis in the rat colon. *Dis Colon Rectum* 1991; **34:** 572-6.
35. Potter JD, McMichael AJ. Diet and cancer of the colon and rectum: a case-control study. *JNCI* 1986; **76:** 557-69.
36. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990; **323:** 1664-72.
37. Tominaga S, Ogawa H, Kuroishi T. *Usefulness of correlation analyses in the epidemiology of stomach cancer. NCI Monogr* 1982; **62:** 135-40.
38. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991; **2:** 325-57.
39. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* 1991; **2:** 427-42.
40. Ministry of Health and Welfare. *The National Nutritional Survey Report (1991)*. Tokyo, Japan: Daiichi-Shuppan, 1993.