

# Tobacco Smoking and Colorectal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population

Tetsuya Mizoue<sup>1</sup>, Manami Inoue<sup>2</sup>, Keitaro Tanaka<sup>3</sup>, Ichiro Tsuji<sup>4</sup>, Kenji Wakai<sup>5</sup>, Chisato Nagata<sup>6</sup>, Shoichiro Tsugane<sup>2</sup> and Research Group for the Development, Evaluation of Cancer Prevention Strategies in Japan

<sup>1</sup>Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka,

<sup>2</sup>Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, <sup>3</sup>Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga,

<sup>4</sup>Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, <sup>5</sup>Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya and

<sup>6</sup>Department of Epidemiology and Preventive Medicine, Gifu University School of Medicine, Gifu, Japan

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**Background:** It is unclear whether tobacco smoking is related to colorectal cancer risk in Japan. We evaluated the association among the Japanese population based on a systematic review of epidemiologic evidence.

**Methods:** Original data were obtained from searches of MEDLINE using PubMed, complemented with manual searches. The evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility as previously evaluated by the International Agency for Research on Cancer.

**Results:** A total of six cohort studies and 15 case-control studies were thus identified. A substantial degree of heterogeneity was observed in the association between smoking and colon cancer; most case-control studies published before 1994 reported an inverse association, whereas studies conducted over the last decade did not find any significant association. Recent cohort studies have shown a non-significant 20–40% increase in colon cancer risk associated with current smoking. Several recent case-control studies and some cohort studies have identified a weak to strong positive association between smoking and rectal cancer.

**Conclusion:** We conclude that tobacco smoking possibly increases the risk of colorectal cancer among the Japanese population. More specifically, tobacco smoking may possibly increase the risk of rectal cancer; however, epidemiologic evidence is still insufficient to demonstrate any clear association with colon cancer.

## INTRODUCTION

In Japan, colorectal cancer has markedly increased over the last several decades (1) and it is now among the highest levels in the world (2). The increase in mortality has been linked to dietary changes including a decreased consumption of dietary fibers (3) or grains (4). However, the increasing male-to-female mortality ratio from colorectal cancer since 1970 in Japan (1) may have been a result of sex differences in health-related lifestyles including tobacco smoking.

Tobacco smoke contains numerous chemicals that are potentially carcinogenic to humans. The range of cancer sites associated with tobacco smoking has been expanded and the International Agency for Research on Cancer (IARC) (5) recently admitted cancers of several sites including stomach and liver as smoke-related. Although colorectal cancer has not formally been recognized as a smoke-related cancer, a review identified emerging evidence showing an increased risk of colorectal cancer associated with smoking, especially long-term smoking (6). However, such an association has been reported mainly from the United States, whereas the findings from other populations remain conflicting.

The objective of the present study was to review the epidemiological findings regarding the association between smoking and colorectal cancer among Japanese population.

For reprints and all correspondence: Tetsuya Mizoue, Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan.  
E-mail: mizoue@phealth.med.kyushu-u.ac.jp

The study results were summarized and the magnitude of the association was assessed. This work was conducted as part of a project of systematic evaluation of the epidemiological evidence regarding lifestyles and cancers in Japanese (7).

## METHODS

The original data for this review were identified by searches of MEDLINE using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between tobacco smoking and colorectal cancer incidence or mortality among Japanese from 1963 to 2004, including papers in press if available, were identified using the search terms 'tobacco smoking', 'colorectal cancer', 'colon cancer', 'rectal cancer', 'cohort studies', 'case-control studies', 'Japan' and 'Japanese' as keywords found in the abstract. Papers written in either English or Japanese were reviewed, and only studies on Japanese population living in Japan were included. The individual results were summarized in the tables separately by a study design as cohort or case-control studies and, if available, by cancer site as colon, rectum or colorectum.

An evaluation was made based on the magnitude of association and the strength of evidence. First, the relative risks in each epidemiologic study were grouped by the magnitude of association, while considering statistical significance (SS) or no statistical significance (NS), as strong,  $<0.5$  or  $>2.0$  (SS); moderate, either (i)  $<0.5$  or  $>2.0$  (NS), (ii)  $>1.5$  to 2 (SS) or (iii) 0.5 to  $<0.67$  (SS); weak, either (i)  $>1.5$  to 2 (NS), (ii) 0.5 to  $<0.67$  (NS) or (iii) 0.67 to 1.5 (SS); or no association, 0.67 to 1.5 (NS). In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included, and the incidence was given priority over mortality as an outcome measure. The incidence was also given priority in a single publication describing both incidence and mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (8), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from IARC (5). Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. When we reach a conclusion that there is 'convincing' or 'probable' evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

## MAIN FEATURES AND COMMENTS

A total of six cohort studies and 15 case-controls studies were identified (Table 1 and Table 2, respectively). Among the

cohort studies, four presented results by gender (10,12–14), one for men only (9), and one only for men and women combined (11). The respective numbers for the case-control studies are three, four and eight. Two case-control studies that did not indicate a point estimate and confidence interval, or  $P$ -value, were excluded (15,27), and a summary of the magnitude of association for the remaining studies is shown in Tables 3 and 4 for the cohort studies and case-control studies, respectively.

Among the five cohort studies showing relative risks separately for the colon and rectum, no study found a significant association with colon cancer, although recent cohort studies (12–14) reported a non-significant 20–40% increased risk for colon cancer associated with smoking. For rectal cancer, one study (10) found a weak positive association in both men and women, whereas another study (12) reported a strong positive association in men. Of the two cohort studies showing relative risk for colon and rectum combined, a nation-wide study (13) reported a weak positive association in men. This study also found marginally significant associations in a separate analysis for the colon and rectum; the respective relative risks (95% confidence intervals) of current smoking compared with never-smoking were 1.4 (0.99–1.9) and 1.4 (0.9–2.3).

Of the 13 case-control studies evaluated, 11 studies provided odds ratios for the colon and rectum separately. Among these studies, five (17–20,22) of six studies published before 1994 have identified a reduced risk of colon cancer associated with smoking, whereas no study published after 1994 showed either a positive or inverse association with colon cancer. For rectal cancer, of five relevant studies published after 1994, four (23–25,29) have shown a weak or moderate positive association and the remaining study (28) reported a significant trend association with smoking index ( $P$  for trend = 0.04), whereas studies published before 1994 did not find any significant association. Of the four case-control studies reporting odds ratio for the colon and rectum combined (16,21,26,28), one study (26) found a significantly increased risk associated with smoking, especially with smoking in the distant past.

Four cohort studies (9,12–14) and two case-control studies (26,29) adjusted for alcohol consumption, but few studies controlled for other dietary (14) and non-dietary factors including sports activities (13,14) and obesity (12–14,26). Three case-control studies were performed on a community basis for recruiting control subjects (20–22), whereas the remaining studies were conducted using either hospital-based, health center-based or screening-based design.

Numerous studies including Japanese one (30) have identified smoking as a risk factor for colorectal adenomas, a precursor of colorectal cancer. Among the Japanese studies reviewed; however, we found a substantial heterogeneity in the risk estimates for an association between smoking and colon cancer, including marginally significant positive association in a nation-wide cohort study (13) and an inverse association in several case-control studies (17–20,22). Interestingly, all case-controls studies that reported an inverse association with colon cancer were published before 1994.

**Table 1.** Tobacco smoking and colorectal cancer risk, cohort study in Japanese population

References	Study period	Study population				Category	Number among cases (95% CI or <i>P</i> )	Relative risk for trend	<i>P</i> for trend	Confounding variables considered
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths					
Kono et al. 1987 (9)	1965–83	5130 men	Male physicians	Death	Large bowel	Never/past	1.00			Age and alcohol drinking
Akiba and Hirayama 1990 (10)	1965–82	265118 (122261 men, Six prefecture cohort of census population) 142857 women)	Death	Colon	Never	Current	NA			
						Up to 19 cigs/day	0.89 (0.42–1.87)			
						20+	0.93 (0.39–2.21)			
						Never	43	1.0	>0.1	Age, residence and occupation
						1–4 cigs/day	3	0.9 (0.2–2.6)		
						5–14	62	1.0 (0.7–1.6)		
						15–24	69	1.2 (0.5–2.4)		
						25–34	8	1.8 (0.6–4.2)		
						35+	5	1.1 (0.8–1.5)		
						Never	232	1.0	>0.1	
						Current	25	0.9 (0.6–1.3)		
						1–4 cigs/day	5	1.1 (0.4–2.4)		
						5–14	18	0.9 (0.5–1.4)		
						15+	2	0.5 (0.1–1.6)		
						Never	50	1.0	0.09	
						Current	204	1.4 (1.0–1.9)		
						1–4 cigs/day	5	1.4 (0.5–3.2)		
						5–14	85	1.3 (0.9–1.9)		
						15–24	101	1.4 (1.0–2.0)		
						25–34	10	1.5 (0.7–2.9)		
						35+	3	1.1 (0.3–2.9)		
						Never	189	1.0	>0.1	
						Current	22	0.9 (0.6–1.5)		
						1–4 cigs/day	2	0.5 (0.1–1.7)		
						5–14	14	0.9 (0.5–1.5)		
						15+	6	2.1 (0.8–4.3)		
						Never		1.0		
Akiba 1994 (11)	1963–87	61505 men and women	RERF Life Span Study (atomic bomb survivors and non-exposed subjects)	Incidence	Colon					City, sex, population group, atomic bomb exposure, year of birth and age
						324 (M: 172; F: 152)	Past	0.9 (0.6–1.4)		
						Current		1.2 (0.9–1.6)		
						Never		1.0		

**Table 1.** *Continued*

References	Study period	Study population			Category	Number among cases	Relative risk (95% CI or <i>P</i> )	<i>P</i> for trend	Confounding variables considered
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths				
Shimizu et al. 2003 (12)	1993–2000	29 051 (13 392 men, 15 659 women)	Residents in Takayama city	Incidence	Colon 104 men	Past Current	16	1.00	0.19
					Up to 20 pack-years >20	41	1.36 (0.79–2.33)		Age, body height, body mass index, alcohol intake and year of education
				Colon	Never	47	1.37 (0.81–2.32)		
			77 women	Never	68	1.00	0.54		
				Current	Up to 10 pack-years >10	4	0.59 (0.21–1.62)		
				Rectum	Never	5	0.77 (0.30–1.96)		
		57 men		Current	Up to 20 pack-years >20	7	1.00	0.04	
				Rectum	Never	16	1.33 (0.57–3.12)		
				38 women	Current	34	2.44 (1.12–5.30)		
					Up to 10 pack-years >10	32	1.00	0.63	
Otani et al. 2003 (13)	1990–99	90 004 (42 540 men, 47 464 women)	JPHC study (cohort I: 5 prefectures, cohort II: 6 prefectures), residential registry	Incidence	Colorectum 447 men	Past	4	1.76 (0.60–5.14)	
				Never	2	0.94 (0.21–4.16)			
				Current	78	1.00			Age, family history of colorectal cancer, body mass index, alcohol consumption, physical exercise and area
				Up to 20 pack-years 20–29	124	1.3 (0.98–1.7)			
				30–39	245	1.4 (1.1–1.8)	0.47 among current smokers		
				40+	33	1.1 (0.8–1.7)			
			Colon	Never	50	1.3 (0.9–1.9)			
		298 men		Past	73	1.4 (1.05–2.0)			
					40+	83	1.4 (0.99–1.8)		
					Never	53	1.00		
					Past	86	1.4 (0.96–1.9)		



**Table 2.** Tobacco smoking and colorectal cancer risk, case-control study in Japanese population

References	Study time	Type and source	Definition	Number of cases	Number of controls	Category	Odds ratio (95% CI or P)	P for trend	Confounding variables considered	Comments
Kondo 1975 (15)	1967-73	Hospital-based (three hospitals in Nagoya)	Case: 91% were histologically confirmed; Control: inpatients without history of cancer of the digestive organs, oral cavity, pharynx, lung, or larynx, or other diseases of the colonrectum	93 men 86 women	406 men* 174 women*	Non-smoker Current 1-20 cigs/day 21+ Non-smoker Smoker 1-10 cigs/day 11+	1.00 0.50 0.66 0.22 1.00 0.52 0.69 0.23	Matched (1 : 2) for age ( $\pm 5$ years) and sex	*Total number of controls for colorectal cancer cases. Number for each site was not shown. Odds ratio was calculated based on numbers of cases and controls presented in table	
Haenszel et al. 1980 (16)	(not described)	Hospital-based (Hiroshima, Aichi, Miyagi)	Case: 89% were histologically confirmed; Control: inpatients without gastric and duodenal ulcers, other disease of the large bowel, or other cancers of the digestive system	284 men and women	571 men and women	Never smoking	1.00	0.21	Matched (1 : 2) for age, sex and hospital (prefecture)	
Watanabe et al. 1984 (17)	1977-83	Hospital-based (five hospitals in Kyoto, Shiga, Hyogo)	Case: histologically confirmed cases; Control: inpatients without history of cancer or any diseases of large bowel	138 men and women	138 men and women	Non-smoker Smoker	0.77 (n.s.)	0.26 (0.13-0.53)	Matched (1 : 1) for hospital, sex and age ( $\pm 5$ years)	

Reference	Year	Setting	Case definition	Control definition	Number of men	Number of women	Exposures	Adjusted OR	95% CI	Notes
								Non-smoker	Smoker	
Tajima and Tominaga 1985 (18)	1981–83	Hospital-based (Aichi Cancer Center)	Case: histologically confirmed cases; Control: inpatients without history of cancer	Colon	65 men and women	65 men and women	Non-smoker Smoker	1.00 0.71 (0.34–1.47)	0.53 (0.31–0.89) 0.46 (0.21–1.03)	Adjusted for age
Kato et al. 1990 (19)	1979–87	Registry-based (Aichi Cancer Registry)	Case: histologically confirmed (90%); Control: cases with smoking-unrelated cancers	Colon	1716 men	16 600 men*	Non-smoker Smoker	1.00 0.78 (0.70–0.88)	*Common controls for cases of cancer of the stomach, colon or rectum	Adjusted for age
				Proximal colon (n = 445)			Non-smoker Smoker	1.00 0.70 (0.57–0.87)		
				Distal colon (n = 765)			Non-smoker Smoker	1.00 0.83 (0.71–0.98)		
				Rectum	16 111 men	16 600 men*	Non-smoker Smoker	1.00 0.93 (0.82–1.05)		

**Table 2.** *Continued*

References	Study time	Type and source	Definition	Study subjects	Category	Odds ratio (95% CI or <i>P</i> )	<i>P</i> for trend	Confounding variables considered	Comments
Kato et al. 1986–90 1990 (20)	1986–90	Population-based (Aichi)	Case: histologically confirmed cases at Aichi Cancer Center Hospital; Control: population controls randomly selected through telephone directories	Colon 132 (M: 79; F: 53) F: 201)*	Never Past Current	578 (M: 377; F: 201)*	1.00 1.12 (0.60–2.10) 0.59 (0.32–1.11)	Adjusted for residence, sex and age (5 year age group)	*Common controls for cases of cancer of the colon and rectum
Yoshida et al. 1992 (21)	1987–90	Population-based (Sapporo)	Case: patients diagnosed at the First Department of Surgery of Sapporo Medical University or its affiliated hospitals; Control: selected from telephone books	Colon 177 (M: 81; F: 96)	Never, past, sometimes Current (everyday)	354 (M: 162; F: 192)	1.00 0.79 (0.51–1.22)	Matched (1 : 2) for sex, sex, age ( $\pm 3$ years) and registered residence	
Hoshiyama et al. 1993 (22)	1984–90	Population-based (Saitama)	Case: histologically confirmed cases at the Saitama Cancer Center Hospital; Control: population controls taken from seven provincial cities and two towns in the vicinity of the hospital	Colon 79 (M: 37; F: 42)	Never, past, sometimes Current (everyday)	653 (M: 343; F: 310)*	1.00 0.89 (0.55–1.45)	Adjusted for sex and age	*Common controls for cases of cancer of the colon and rectum

Rectum								
102 (M: 61; F: 41)	653 (M: 343; F: 310)*	Never	1.0					
		Past	1.4 (0.6-3.1)					
		Current						
		1-20 cigs/day	1.7 (0.9-3.1)					
		30+	1.0 (0.3-2.6)					
Kotake et al. 1995 (23)	Hospital-based (10 hospitals in Kanto region)	Cigarette years	Never (0)	1.0	0.31			
			Up to 800 cig-years	1.6 (0.8-3.0)				
			>800	1.5 (0.6-3.6)				
Colon								
Case: histologically confirmed cases; Control: screening controls and hospital controls, including cancer patients	187 (M: 111; F: 76)	187 (M: 111; F: 76)	Never	1.0				
Rectum								
176 (M: 103; F: 73)	176 (M: 103; F: 73)	Never	1.0					
		Past	—					
		Current	1.3 (0.3-5.2)					
		Cigarette years	Never (0)	1.0				
			Up to 400 cig-years	—				
			>400	0.8 (0.2-2.8)				
Colon: proximal								
Case: histologically confirmed cases; Control: first-visit outpatients free from cancer	51 men	8621 men*	Never	1.0				
			Ever (habitual)	0.7 (0.5-1.4)				
			Never	1.0				
			Ever (habitual)	0.9 (0.4-2.4)				
Colon: distal								
75 men	8621 men*	Never	1.0					
		Ever (habitual)	1.0 (0.6-1.7)					
		Never	1.0					
		Ever (habitual)	1.1 (0.6-2.3)					

\*Common controls  
for cases of cancer  
of the colon and  
rectum

Adjusted for age

Table 2. Continued

References	Study time	Type and source	Definition	Study subjects	Category	Odds ratio (95% CI or <i>P</i> )	<i>P</i> for trend	Confounding variables considered	Comments
Murata et al. 1996 (25)	1984-93	Screening-based (participants of stomach cancer screening)	Case: confirmed by a record linkage to cancer registry data; Control: screenees free from any cancer during the follow-up period	Rectum 131 men 70 women	8621 men* 23 161 women*	Never Ever (habitual) Never Ever (habitual)	1.0 1.9 (1.1-3.2) 1.0 1.7 (1.0-3.1)		
Yamada et al. 1997 (26)	1991-93	Health check-up based JPL Tokyo Health Care Center; multiphasic health check-up program	Case: histologically confirmed cases; Control: examinees without history of colorectal cancer and inflammatory bowel disease	Rectum 61 men 66 (M: 55; F: 11)	122 men 132 (M: 110; F: 22)	Non-smoker* Never	1.0 1.0	Matched (1 : 2) for sex, birth year (<2 years) and residence	*Non-smoker, including lifetime never-smoker and past smoker (who had quit for 2 years or more); smoker, including those who had quit smoking within the past 2 years
				Smoker* 1-10 cigs/day 11-20 21+	n.s.	0.8 (n.s.) 1.1 (n.s.) 1.0 (n.s.)			
				Rectum 43 men 86 men	Non-smoker n.s.	1.0			
				Smoker 1-10 cigs/day 11-20 21+	Smoker n.s.	1.3 (n.s.) 1.1 (n.s.) 3.0 (n.s.)			
				Colorectum 66 (M: 55; F: 11)					Results for carcinoma <i>in situ</i> ( <i>n</i> = 129) were also presented
							0.8	Matched (1 : 2) for sex, age and history of previous health check-up at the Center; Adjusted for body mass index and alcohol consumption	

			Past	1.8 (0.7-4.4)			
		Current					
	1-15 cigs/day			1.2 (0.4-3.8)			
	16-30			0.8 (0.3-2.1)			
	31+			2.4 (0.7-8.6)			
	Pack-years						
	0 pack-year			1.0			
	1-20			0.8 (0.3-2.2)			
	21-40			1.2 (0.5-3.0)			
	41+			2.6 (0.9-7.1)			
	Within the past 20 years						
	0 pack-year			1.0	0.1		
	1-15			1.1 (0.5-2.7)			
	16-30			1.2 (0.5-2.9)			
	31+			2.9 (0.9-9.4)			
	Until 20 years ago						
	0 pack-year			1.0	0.005		
	1-15			1.0 (0.4-2.4)			
	16-30			3.4 (1.2-9.2)			
	31+			5.0 (1.3-18.3)			
Ping et al. 1998 (27)	1986-94	Health check-up based (Tokai University Hospital; source: health check-up examinees at the hospital)	Case: histologically confirmed cases; Control: cancer-free examinees	Colorectum	Matched (1 : 3) for sex, age ( $\pm 2$ years), date of health checking ( $\pm 3$ months) and residence; excluded 35 controls owing to the lack of information on lifestyle		
Murata et al. 1999 (28)	1989-97	Hospital-based case-control study (Chiba Cancer Center Hospital)	Case: those who underwent surgery; Control: outpatients free from cancer	Colorectum	*Odds ratio (not presented in the paper) was calculated according to figures in table. Description of method is unclear		
	267 men	265 men and women	100 (M: 77; F: 23)	Never	1.0		
				Past	1.4*		
				Current	1.5*		
	267 men	395 men	Smoker				
			<20 cigs/day	1.03 (0.64-1.6)			
			20-29	1.20 (0.80-1.8)			
			30+	1.16 (0.73-1.8)			
	Colon	157 men	Non-smoker	1.00	0.1	Adjusted for age (10 year age group)	

**Table 2.** *Continued*

References	Study time	Type and source	Definition	Number of cases	Number of controls	Category	Odds ratio (95% CI or <i>P</i> )	<i>P</i> for trend	Confounding variables considered	Comments
Minami et al. 2003 (29)	1997–2001	Hospital-based case-control study (Miyagi Cancer Center Hospital)	Case: clinical, cytological and/or histopathological examination; Control: non-cancer patients	110 men 395 men	395 men	Smoker Non-smoker	<20 cigs/day 20–29 30+	0.93 (0.54–1.6) 1.09 (0.68–1.8) 0.96 (0.55–1.7)	0.04	
						Smoker	<20 cigs/day 20–29 30+	1.17 (0.60–2.3) 1.40 (0.77–2.5) 1.50 (0.82–2.7)		
										Adjusted for age, year of survey, alcohol consumption, family history of index cancer in parents and siblings and occupation
				184 men	1222 men	Never Past Current	1.00 0.92 (0.59–1.42) 0.90 (0.60–1.35)			
				140 women	1222 women	Never Past Current	1.00 1.13 (0.38–3.38) 1.16 (0.60–2.23)			
				104 men	1222 men	Never Past Current	1.00 1.44 (0.76–2.73) 1.67 (0.93–3.00)			
				60 women	1222 women	Never Past Current	1.00 2.12 (0.61–7.34) 1.79 (0.82–3.93)			

**Table 3.** Summary of the association between tobacco smoking and colorectal cancer risk, cohort study

References	Study period	Sex	Number of subjects	Age	Event	Number of incident cases or deaths	Magnitude of association*		
							Colon	Rectum	Colorectum
Kono et al. 1987 (9)	1965–83	Men	5477	27–89 years	Death	39	NA	NA	–
Akiba and Hirayama 1990 (10)	1966–81	Men	122 261	40+ years	Death	444	–	↑	NA
		Women	142 857	40+ years	Death	468	–	↑	NA
Akiba 1994 (11)	1963–87	Men and women	61 505	Not specified	Incidence	542	–	–	NA
Shimizu et al. 2003 (12)	1993–2000	Men	13 392	35+ years	Incidence	161	–	↑↑	NA
		Women	15 659	35+ years	Incidence	134	–	–	–
Otani et al. 2003 (13)	1990–99	Men	42 540	40–69 years	Incidence	447	–	–	↑
		Women	47 464	40–69 years	Incidence	259	NA	NA	–
Wakai et al. 2003 (14)	1988–97	Men	25 260	40–79 years	Incidence	366	–	–	NA
		Women	34 619	40–79 years	Incidence	246	–	–	NA

NA, not available.

\*↑↑↑ or ↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition).

Giovannucci (6) proposed a hypothesis that smoking is involved in cancer initiation and long induction period is needed before the appearance of the carcinogenic effects of smoking, which may be detected by recent studies including a sufficient number of long-term smokers. In line with the hypothesis, recent cohort studies in Japan (12–14) reported a 20–40% increased risk of colon cancer associated with current smoking in men. These studies probably include many long-term smokers, because most Japanese smokers started smoking around 20 years of age and participants in these studies were relatively old: 35 years or older (12), 40–69 years (13) and 40–79 years (14).

We identified a significant, or marginally significant, increased risk of rectal cancer associated with smoking in all case-control studies published after 1994 (23–29) and in some cohort studies (10,12,13). No study in this review reported a significant inverse association between smoking and rectal cancer. A clearer association of smoking with rectal cancer than with colon cancer has also been noted in several studies outside Japan (6). Furthermore, a Japanese study indicated that smoking is more strongly associated with rectal adenomas than with colon adenomas (30).

We should mention methodological issues. Several Japanese studies (9,12–14,26,29) controlled for alcohol drinking, a probable risk factor for colorectal cancer (8) and closely correlated with smoking behavior. However, few controlled for other dietary factors (14). According to a Japanese national survey on nutrition (31), there is a substantial difference between smokers and non-smokers in diet including the intake of calcium and folate, which are potentially associated with reduced risk of colorectal cancer (32,33). As a result, such confounding cannot be excluded from the results of Japanese studies.

In summary, epidemiological evidence for the association with smoking among Japanese population appears to be stronger for rectal cancer than for colon cancer. A consistent positive association between smoking and rectal cancer was observed among several recent case-control studies. However, since earlier case-controls studies and several cohort studies did not show a significant association between smoking and rectal cancer, it would therefore be appropriate to classify their association as ‘possible’. For colon cancer, epidemiological studies have provided mixed results; namely, several earlier case-control studies reported a decreased risk with smoking, whereas recent cohort studies showed a non-significant increased risk with smoking. Therefore, evidence among Japanese population is insufficient to establish any clear association between smoking and colon cancer.

## EVALUATION OF THE EVIDENCE ON TOBACCO SMOKING AND COLORECTAL CANCER RISK IN JAPANESE

From these results and based on assumed biological plausibility, we conclude that tobacco smoking may possibly increase the risk of colorectal cancer among the Japanese population.

**Table 4.** Summary of the association between tobacco smoking and colorectal cancer risk, case-control study

References	Study period	Study subjects			Magnitude of association*		
		Sex	Age	Number of cases	Number of controls	Colon	Rectum
Haenszel et al. 1980 (16)	NA	Men and women	Not specified	284	571	NA	—
Watanabe et al. 1984 (17)	1977–83	Men and women	Not specified	203 (M: 110, F: 93)	203 (M: 110, F: 93)	↓↓	—
Tajima et al. 1985 (18)	1981–83	Men	40–79 year	52	111	↓	—
Kato et al. 1990 (19)	1979–87	Men	20 yr or older	3327	16600	↓	—
Kato et al. 1990 (20)	1986–90	Men and women	Not specified	223	578	↓	—
Yoshida et al. 1992 (21)	1987–90	Men and women	25–79 year	330 (M: 171, F: 159)	660	—	—
Hoshiyama et al. 1993 (22)	1984–90	Men and women	40–69 year	181 (M: 98, F: 83)	653 (M: 343, F: 310)	↓↓	—
Kotake et al. 1995 (23)	1992–94	Men and women	Not specified	363 (M: 214, F: 149)	363 (M: 214, F: 149)	—	↑↑
Inoue et al. 1995 (24)	1988–92	Men	Not specified	257	8621	—	↑↑
		Women	Not specified	175	23161	—	NA
Murata et al. 1996 (25)	1984–93	Men	Not specified	104	208	—	↑↑
Yamada et al. 1997 (26)	1991–93	Men and women	34–80 year	66 (M: 55, F: 11)	132 (M: 110, F: 22)	NA	↑↑
Murata et al. 1999 (28)	1989–97	Men	Not specified	267	395	—	—
Minami et al. 2003 (29)	1997–2001	Men	40 year or older	288	1222	—	↑
		Women	40 year or older	200	1222	—	NA

NA, not available

\*↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate, ↑ or ↓, weak; —, no association (see text for more detailed definition).

More specifically, tobacco smoking may possibly increase the risk of rectal cancer; however, the epidemiologic evidence remains insufficient to demonstrate any clear association with colon cancer.

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