Table 3. Cigarette smoking and esophageal cancer risk, case–control studies among Japanese population

Author	Reference	Study period	Subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
			Type and source	Definition	Number of cases	Number of controls					
Nakachi et al.	25	1973–85	Population-based	Cases: those who died of cancer of esophagus identified from death certificates Controls: those selected from Electoral Roll in the same area	343 (257 males and 86 females) (mean age: 68.3 male, 71.9 female)	343 (257 males and 86 females) (mean age: 68.2 male, 71.5 female)	Cumulative number of cigarettes Never <400 000 cigarettes ≥400 000 cigarettes[a]	 1.0 1.142 (0.685–1.904) 2.521 (1.230–5.166)	Not described	Matched for age, sex and neighborhood Not adjusted	
Sasaki et al.	26	1974–79	Hospital-based (three major hospitals in Nagoya and two in Wakayama)	Case: esophageal cancer patients who admitted to hospitals Controls: non-digestive tract cancer patients	201 (91 males and 28 females in Nagoya, 54 males and 28 females in Wakayama) (age not described)	403 (170 males and 86 females in Nagoya, 115 males and 61 females in Wakayama) (age not described)	Smoking status Nagoya (males) Non-smoker Smoker[a] Nagoya (females) Non-smoker Smoker Wakayama (males) Non-smoker Smoker Wakayama (females) Non-smoker Smoker[a]	 1.0 5.0 (2.1–11.8) 1.0 0.9 (0.3–2.6) 1.0 4.3 (1.7–11.3) 1.0 2.3 (0.8–6.8)	Not described	Matched for age, sex, hospital and time of admission Adjusted for age	
Hanaoka et al.	27	1989–91	Hospital-based (seven hospitals: Keio University, Iwate Medical College, Kurume University, Chiba University, National Shikoku Cancer Center, Aichi Cancer Center, Tokyo Women's Medical College)	Cases: male inpatients histologically diagnosed as having primary esophageal cancer Controls: male inpatients with diseases other than lung cancer, laryngeal cancer, hepatocellular carcinoma, pulmonary emphysema and chronic pancreatitis	141 (male only) (age not described)	141 (male only) (age not described) (90 with malignant neoplasms, 51 with benign diseases)	Tobacco consumption Never smoked Ex/light smoker Moderate smoker Moderate-to-heavy smoker[a] Heavy smoker	 1.0 1.24 (0.59–2.63) 1.41 (0.62–3.9) 1.52 (0.77–3.01) 1.03 (0.49–2.16)	0.55	Matched for age, sex and prefecture of residence Adjusted for alcohol consumption	Light smoker: <5 cigarettes/day, moderate smoker: 5≤cigarettes/day<15, moderate-to-heavy smoker: 15≤cigarettes/day<25, heavy smoker: ≥25 cigarettes/day
Takezaki et al.	28	1988–97	Hospital-based (Aichi Cancer Center Hospital)	Cases: first-visit male outpatients diagnosed as having primary cancer of esophagus Controls: first-visit male outpatients confirmed to be cancer-free	284 males (40–79 years old)	11 936 males (40–79 years old)	Smoking status Never Former Current[a] Number of cigarettes in current smokers Never 1–19/day ≥20/day Years of smoking in current smokers Never 1–29 ≥30 Age when started smoking in current smokers Never <20 years ≥20 years Years after quitting in former smokers Never 1–9 ≥10	 1.0 1.6 (0.9–2.8) 3.5 (2.1–5.8) 1.0 3.1 (1.8–5.5) 3.5 (2.1–5.9) 1.0 2.2 (1.1–4.4) 3.6 (2.1–6.0) 1.0 3.9 (2.2–6.9) 3.3 (1.9–5.5) 1.0 2.3 (1.3–4.2) 1.3 (0.7–2.3)	Not described	Not matched Adjusted for age, season of visit, drinking and consumption of raw vegetables	

Continued

Table 3. *Continued*

Author	Reference	Study period	Subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
			Type and source	Definition	Number of cases	Number of controls					
Matsuo et al.	29	1999–2000	Hospital-based (Aichi Cancer Center Hospital)	Cases: outpatients first diagnosed as having esophageal cancer Controls: outpatients without a history of cancer	102 (86 males and 16 females) (40–76 years old)	241 (118 males and 123 females) (39–69 years old)	Smoking Never Former Current PYs ≤50 PYs >50[a]	 1.0 3.19 (1.34–7.58) 9.78 (4.49–21.3) 7.27 (3.17–16.7) 17.2 (6.61–44.7)	Not described	Adjusted for age and sex	
Tsuda et al.	30	1986–93	Population-based (Okayama Tobi area)	Cases: those who died with esophageal cancer identified by death certificates Controls: those who died with colon, pancreas, bladder and other urinary cancers	22 (age and sex not described)	198 (age and sex not described)	Smoking status Non-smoker Ex-smoker[a] Smoker	 1.0 6.59 (0.57–335.7) 3.50 (0.50–151.4)	Not described	Not adjusted	
Yokoyama et al.	31	2000–01	Hospital-based (National Cancer Center Hospital, National Cancer Center Hospital East, Kawasaki Municipal Hospital, National Osaka Hospital)	Cases: those with esophageal squamous cell carcinomas diagnosed by histology within 3 years of registration Controls: cancer-free males visited two Tokyo Clinics for annual health checkups	234 males (40–79 years old)	634 males (40–79 years old)	Smoking (pack-years) <30 ≥30[a]	 1.0 2.44 (1.55–3.84)	Not described	Not matched Adjusted for ALDH2, ADH2 and ADH3 genotypes, alcohol drinking, strong alcohol beverage, green-yellow vegetables and fruits	
Takagi et al.	32	1990–99	Hospital-based (Osaka Medical Center)	Cases: hospitalized female patients with esophageal cancer Controls: hospitalized female patients without cancer, benign tumor, cardiovascular disease and alcoholic liver disease	34 females (mean age: 63.4)	178 females (mean age: 53.1)	Smoking status Never Ever[a]	 1.0 1.7 (0.7–4.3)	Not described	Adjusted for age, alcohol drinking, hot food preference, tooth brushing	
Yokoyama et al.	33	2000–04	Hospital-based (National Cancer Center, National Cancer Center East, Kawasaki Municipal hospital, National Osaka Hospital)	Cases: female patients with esophageal squamous cell carcinoma within 3 years of their registration Controls: cancer-free females visited two clinics for annual health checkups	52 females (40–79 years old)	412 females (40–79 years old)	Smoking (pack-years) 0 <30 30+[a]	 1.0 3.89 (1.85–8.18) 5.12 (2.02–13.0)	0.0001	Adjusted for age	
Akiyama et al.	34	1997–2008	Hospital-based (Yokohama City University Hospital)	Cases: diagnosed as having esophageal squamous cell carcinoma Controls: patients who had undergone endoscopies as part of a health checkup	253 (225 males and 28 females) (38–86 years old)	254 (225 males and 28 females) (38–87 years old)	Smoking habit[a]	3.231 (2.062–5.063)	0.0001	Age/sex group matched	The detail of smoking habit was not described
Oze et al.	35	2001–05	Hospital-based (Aichi Cancer Center Hospital)	Cases: histologically confirmed esophageal cancer cases Controls: non-cancer first-visit outpatients at the same hospital	265 (235 males and 30 females) (33–79 years old)	530 (470 males and 60 females) (36–78 years old)	Pack-years PY < 5 5 ≤ PY < 20 20 ≤ PY < 40 PY ≥ 40[a]	 1.00 2.92 (1.31–6.50) 4.96 (2.51–9.81) 7.02 (3.58–13.77)	Not described	Age/sex matched Adjusted for alcohol consumption, ALDH2 genotype, fruit and vegetable intake, hot beverage intake, BMI	

[a]Categories from which the magnitude of association was judged.

Table 4. Summary of the association between cigarette smoking and esophageal cancer risk, cohort study

Author	Study period	Study population					Category	Magnitude of association
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths		
Hirayama	1965–81	Male	122 261	≥40	Death	438	Number of cigarettes/day	↑↑↑
		Female	142 857	≥40	Death	147	Number of cigarettes/day	↑↑
Sakata et al.	1988–99	Male	46 465	40–79	Death	100	Years of smoking	↑↑↑
Ishikawa et al.	Cohort 1 (1984–92)	Male	9008	≥40	Incidence	38	Category of smoking	↑↑↑
	Cohort 2 (1990–97)	Male	17 715	40–64	Incidence	40		
Ishiguro et al.	Cohort 1 (1993–2004)	Male	60 876	40–69	Incidence	215	Pack-years	↑↑↑
	Cohort 2 (1995–2004)							

↑↑↑, strong positive association; ↑↑, moderate positive association.

Table 5. Summary of the association between cigarette smoking and esophageal cancer risk, case–control study

Author	Study period	Study subjects				Category	Magnitude of association
		Sex	Age range (years)	Number of cases	Number of controls		
Nakachi et al.	1973–85	Male and female	Not specified	343 (M: 257, F: 86)	343 (M: 257, F: 86)	Cumulative number of cigarettes	↑↑↑
Sasaki et al.	1974–79	Male	Not specified	145	285	Smoking status	↑↑↑
		Female	Not specified	56	118	Smoking status	↑↑
Hanaoka et al.	1989–91	Male	Not specified	141	141	Tobacco consumption	↑
Takezaki et al.	1988–97	Male	40–79	346	11936	Smoking status	↑↑↑
Matsuo et al.	1999–2000	Male and female	40–76	102 (M: 86, F: 16)	241 (M: 118, F: 123)	Smoking	↑↑↑
Tsuda et al.	1986–93	Male and female	Not specified	22	98	Smoking status	↑↑
Yokoyama et al.	2000–01	Male	40–79	234	634	Smoking (pack-years)	↑↑↑
Takagi et al.	1990–99	Female	17–87	34	178	Smoking status	↑
Yokoyama et al.	2000–04	Female	40–79	52	412	Smoking (pack-years)	↑↑↑
Akiyama et al.	1997–2008	Male and female	38–86	265 (M: 235, F: 30)	530 (M: 470, F: 60)	Smoking habit	↑↑↑
Oze et al.	2001–05	Male and female	33–79	742 (M: 641, F: 101)	820 (M: 506, F: 314)	Pack-years	↑↑↑

↑↑↑, strong positive association; ↑↑, moderate positive association; ↑, weak positive association.

Author	Reference	Year	Design	Sex	Ever smoking RR	95% CI	% weight
Hirayama	20	1990	Cohort	M F	2.17	1.80 – 2.61	11.78
Sakata et al.	21	2005	Cohort	M	3.51	1.98 – 6.22	7.97
Ishikawa et al.	22	2006	Cohort	M	3.86	2.07 – 7.22	7.46
Ishiguro et al.	23	2009	Cohort	M	3.48	2.29 – 5.30	9.59
Nakachi et al.	24	1988	Case–control	M F	2.52	1.23 – 5.17	6.62
Sasaki et al.	25	1990	Case–control	M F	2.90	1.78 – 4.72	8.87
Hanaoka et al.	26	1994	Case–control	M	1.29	0.89 – 1.87	10.10
Takezaki et al.	27	2000	Case–control	M	2.39	1.11 – 5.15	6.21
Matsuo et al.	28	2001	Case–control	M F	5.93	3.32 – 10.59	7.92
Tsuda et al.	29	2001	Case–control	M F	4.47	0.98 – 20.51	2.50
Takagi et al.	31	2003	Case–control	F	1.70	0.70 – 4.13	5.31
Yokoyama et al.	32	2006	Case–control	F	4.75	2.15 – 10.50	6.00
Oze et al.	34	2010	Case–control	M F	4.91	3.26 – 7.41	9.67
Summary estimates (random-effect model)					3.01	2.30 – 3.94	100.00
(test for heterogeneity: Q=42.59 with df=12, P<0.001)							

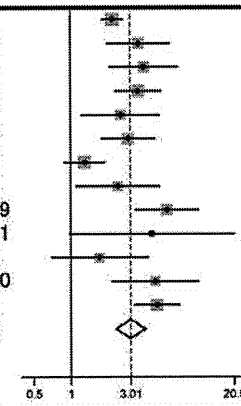

Figure 1. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

Author	Reference	Year	Design	Sex	Current smoking RR	95% CI	% weight
Sakata et al.	21	2005	Cohort	M	4.36	2.00 – 9.51	14.24
Ishikawa et al.	22	2006	Cohort	M	5.05	2.39 – 10.67	14.56
Ishiguro et al.	23	2009	Cohort	M	3.69	2.07 – 6.58	16.38
Hanaoka et al.	26	1994	Case–control	M	1.31	0.85 – 2.01	17.87
Takezaki et al.	27	2000	Case–control	M	3.50	2.10 – 5.83	17.07
Matsuo et al.	28	2001	Case–control	M F	9.78	4.49 – 21.30	14.24
Tsuda et al.	29	2001	Case–control	M F	3.50	0.50 – 24.50	5.64
Summary estimates (random-effect model)					3.73	2.16 – 6.43	100.00
(test for heterogeneity: Q=26.85 with df=6, P<0.001)							

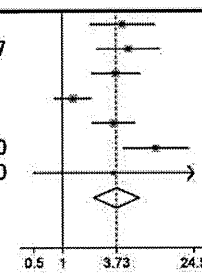

Figure 2. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

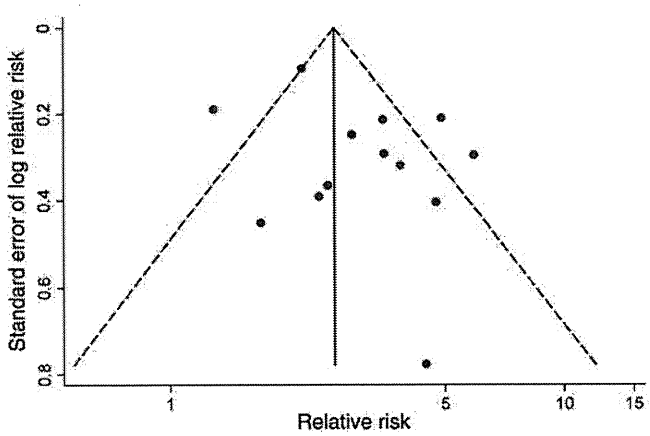

Figure 3. Funnel plot with 95% confidence limits.

Acknowledgements

I.O. is an Awardee of Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the 3rd Term Comprehensive 10-year Strategy for Cancer Control.

Funding

This study was supported by Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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Appendix

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(1)2–13
doi:10.1093/jjco/hyr160
Advance Access Publication 7 November 2011

Review Article

Physical Activity and Colorectal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Received August 31, 2011; accepted October 11, 2011

Objective: Higher levels of physical activity have been consistently associated with a decreased risk of colon cancer, but not rectal cancer, in Western populations. The present study systematically evaluated epidemiologic evidence on the association between physical activity and colorectal cancer risk among the Japanese population.
Methods: Original data were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented by manual searches. The associations were evaluated based on the strength of evidence, the magnitude of association and biologic plausibility.
Results: Two cohort studies and six case–control studies were identified. A weak to strong protective association between physical activity and colon cancer risk was observed in both cohort studies, showing a graded relationship, and among the majority of case–control studies, with some showing a dose–response relationship. The association observed in cohort studies was more consistent and stronger in men than in women and for proximal colon cancer than for distal colon cancer. A protective association with rectal cancer was found only in case–control studies, but the evidence was less consistent and weaker than that observed for colon cancer.
Conclusions: Physical activity probably decreases the risk of colorectal cancer among the Japanese population. More specifically, the evidence for the colon is probable, whereas that for the rectum is insufficient.

Key words: systematic review – epidemiology – physical activity – colorectal cancer – Japanese

INTRODUCTION

Colorectal cancer is a common form of malignancy in developed countries, being the second and third leading cause of cancer death in men and women, respectively (1). In Japan, colorectal cancer mortality has risen remarkably over the past three decades (1970–2000) (2) and its incidence is

among the highest levels worldwide (3). The increasing trend has been attributed to the changes in lifestyles, especially diet featured by a high intake of animal fats and meat and a low intake of fibers and cereals (4,5). Less attention has been paid to decreased physical activity in modern life as a causal factor that could account for the increased colorectal cancer among Japanese.

Physical activity in relation to colorectal cancer has been extensively investigated (6–10). On the basis of a comprehensive review of epidemiologic studies, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AIR) (7) concluded that physical activity convincingly reduces colorectal cancer risk; more specifically, the evidence is stronger for the colon than for the rectum. An earlier systematic review and meta-analysis (6) reported a consistent association between physical activity and a decreased risk of colon cancer; however, no association with rectal cancer was observed. Likewise, several recent systematic reviews and meta-analyses (8–10) consistently reported an inverse association of physical activity with colon cancer risk, but not with rectal cancer (8,9). Briefly, there is ample evidence that physical activity is convincingly associated with a reduced risk of colon cancer, but weaker or absent for rectal cancer. However, such evidence has been mainly derived from studies in Western countries and less is known in Asian countries, including Japan.

To assess the strength and consistency of the association between physical activity and colorectal cancer risk among the Japanese population, we conducted a systematic review of epidemiologic studies on this issue in Japan. This is one in a series of articles that summarized epidemiologic evidence on the relationship of lifestyles to total cancers and major forms of cancer in Japan (11,12).

PATIENTS AND METHODS

This review was based on a MEDLINE search of all published epidemiological studies on the association between physical activity and colorectal cancer incidence or mortality among Japanese published through May 2011. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also done to identify the studies written in Japanese. These methods of literature identification were complemented by manual searches of references from relevant articles where necessary. We employed the terms 'physical activity', 'sports', 'colorectal cancer', 'colon cancer', 'rectal cancer', 'case–control studies', 'cohort studies', 'Japan' and 'Japanese'. Articles written in either English or Japanese were reviewed. Only studies on Japanese populations living in Japan were included. Individual results were summarized in tables separately according to study design as cohort or case–control studies.

The studies were evaluated on the basis of the magnitude of association and the strength of evidence. First, relative risks or odds ratios in each epidemiologic study were grouped by the magnitude of association, considering statistical significance (SS) or no statistical significance (NS), into: strong (symbol ↑↑↑ or ↓↓↓), <0.5 or >2.0 (SS); moderate (symbol ↑↑ or ↓↓), either (a) <0.5 or >2.0 (NS), (b) >1.5–2.0 (SS) or (c) 0.5 to <0.67 (SS); weak (symbol ↑ or ↓), either (a) >1.5–2.0 (NS), (b) 0.5 to <0.67 (NS) or (c) 0.67–1.5 (SS) or no association (symbol −), 0.67–1.5 (NS). We thus defined, for individual study, the magnitude of association by its strength, i.e. the size of relative risks or odds ratios for the highest physical activity group compared with the lowest, and its SS. Two-sided P values <0.05 were considered statistically significant. In case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most recent results were included and the incidence was preferable as the measure of outcome to mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (13), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility based on evidence in experimental models, human studies and other relevant data. Despite 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 was made based on a consensus of the research group members, and it was therefore not necessarily objective.

Main Features and Comments

A total of two cohort studies (14,15) and six case–control studies (16–21) were identified (Tables 1 and 2, respectively). Both cohort studies presented results separately for men and women. Among the case–control studies, two studies presented results by sex (19,21), one for men only (16) and the remaining three studies for men and women combined (17,18,20). The magnitude of association of physical activity with colorectal cancer is summarized in Tables 3 and 4 for cohort studies and case–control studies, respectively.

The two identified cohort studies showed relative risk for each the colon and the rectum. In men, the Japan Public Health Center-based Prospective study (JPHC) (14) found a strong inverse association of physical activity with proximal colon cancer and the other, the Miyagi cohort study (15), reported a strong inverse association with colon cancer. In women, however, physical activity was only weakly related to decreased risk of proximal colon cancer in the JPHC study or was not associated with colon cancer risk in the Miyagi cohort study. For rectal cancer, a moderate positive association was observed in women in the JPHC study, whereas no association was found in women of the Miyagi cohort study or in men of each study. When colon and rectal cancer combined, a weak (14) or moderate (15) inverse association was observed in men, while no association existed in women.

Of the six case–control studies evaluated, five (16–19,21) measured odds ratios for the colon and rectum separately, and one study (20) showed values for the combined colon and rectum only. Of these, two (16,17) found a moderate protective

Table 1. Physical activity and colorectal cancer risk, cohort study among Japanese populations

Reference	Study period	Study population				Category	No. among cases or deaths	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths					
Lee et al. (14)	1995–02	65 022 (29 842 men, 35 180 women)	JPHC study (Cohort I: five prefectures, Cohort II: six prefectures), residential registry	Incidence	Colorectum	MET hours per day[a]				Age, study area, family history of colorectal cancer, smoking, alcohol intake, body mass index, intake of red meat, dietary fiber and folate
					290 men	Lowest	84	1.00		
						Second	81	0.99 (0.72–1.35)		
						Third	64	0.85 (0.61–1.20)		
						Highest	61	0.69 (0.49–0.97)	0.02	
					196 women	Lowest	53	1.00		
						Second	53	1.17 (0.79–1.75)		
						Third	45	0.97 (0.63–1.47)		
						Highest	45	1.16 (0.76–1.77)	0.57	
					Colon					
					197 men	Lowest	64	1.00		
						Second	55	0.87 (0.61–1.26)		
						Third	38	0.62 (0.41–0.95)		
						Highest	40	0.58 (0.39–0.87)	0.006	
					140 women	Lowest	41	1.00		
						Second	37	1.03 (0.65–1.64)		
						Third	35	0.91 (0.57–1.47)		
						Highest	27	0.89 (0.24–1.26)	0.61	
					Proximal colon					
					82 men	Lowest	29	1.00		
						Second	27	0.89 (0.52–1.51)		
						Third	15	0.44 (0.22–0.86)		
						Highest	11	0.29 (0.14–0.60)	<0.001	
					72 women	Lowest	21	1.00		
						Second	21	1.14 (0.61–2.12)		
						Third	21	1.01 (0.53–1.89)		
						Highest	9	0.55 (0.24–1.26)	0.15	
					Distal colon					

					107 men	Lowest	32	1.00		
						Second	27	0.92 (0.54–1.54)		
						Third	20	0.75 (0.42–1.33)		
						Highest	28	0.89 (0.53–1.51)	0.69	
					59 women	Lowest	17	1.00		
						Second	15	1.09 (0.52–2.29)		
						Third	11	0.77 (0.34–1.74)		
						Highest	16	1.37 (0.66–2.85)	0.40	
					Rectum					
					92 men	Lowest	20	1.00		
						Second	26	1.36 (0.74–2.49)		
						Third	26	1.64 (0.90–2.99)		
						Highest	21	1.06 (0.56–2.00)	0.97	
					56 women	Lowest	12	1.00		
						Second	16	1.72 (0.76–3.89)		
						Third	10	1.20 (0.49–2.95)		
						Highest	18	2.23 (0.99–5.01)	0.06	
Takahashi et al. (15)	1990–97	41 988 (20 519 men, 21 469 women)	Miyagi study (Miyagi prefecture)	Incidence	Colorectum	Hours per day[b]				Age, smoking, alcohol intake, body mass index, family history of colorectal cancer, education, sports or exercise, meat intake, intakes of green or yellow vegetables and oranges
					166 men	<0.5	55	1.00		
						0.5–1	51	1.06 (0.72–1.57)		
						>1	60	0.57 (0.38–0.83)	0.003	
					94 women	<0.5	23	1.00		
						0.5–1	29	1.32 (0.76–2.30)		
						>1	42	1.02 (0.60–1.75)	0.91	
					Colon					
					101 men	<0.5	40	1.00		
						0.5–1	30	0.81 (0.50–1.32)		
						>1	31	0.38 (0.23–0.64)	<0.001	
					50 women	<0.5	10	1.00		
						0.5–1	15	1.78 (0.77–4.10)		
						>1	25	1.33 (0.60–2.94)	0.63	
					Rectum					

Continued

Table 1. *Continued*

Reference	Study period	Study population: No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths	Category	No. among cases or deaths	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
					65 men	<0.5	15	1.00		
						0.5–1	21	1.75 (0.88–3.50)		
						>1	29	1.07 (0.55–2.06)	0.94	
					44 women	<0.5	13	1.00		
						0.5–1	14	1.18 (0.54–2.58)		
						>1	17	0.82 (0.39–1.71)	0.55	

[a]Estimated from four levels of physical activity: heavy physical work or strenuous exercise, walking and standing, sedentary and sleep or others.
[b]Estimated from time spent on walking.

association of physical activity against colon cancer, one (19) showed a weak protective association with proximal colon cancer and another (21) exhibited a moderate to strong protective association with distal colon cancer. A protective association was also observed for rectal cancer, although the association was generally less evident than for colon cancer (16–18,21). The remaining study examining the combined colon and rectal cancer only showed no association (20).

We should discuss several methodological issues regarding the evidence of the relationship between physical activity and colorectal cancer in general and in particular for Japanese studies. First, we did not conduct a meta-analysis to calculate summary effect size of the association between physical activity and risk of colorectal cancer. This is because we found a large discrepancy among the studies reviewed here regarding methods used in the ascertainment of physical activity and categories created to group study participants. Secondly, attention should be focused when interpreting the findings of case–control studies. Case–control studies are prone to recall bias, leading to a difference in reported levels of physical activity between cases and controls. Specifically, a protective association between physical activity and colorectal cancer is overestimated if patients with colorectal cancer tend to underreport physical activity in the past, due to the influence of their disease status on recall, compared with healthy control individuals. Thirdly, most of the case–control studies reviewed in the present paper selected controls from among patients or participants of health checkups or screening, which might have resulted in various extents of selection bias among studies. Fourthly, few case–control studies have controlled for factors including intakes of dietary fiber, folate and vegetables, which have been favorably associated with colorectal cancer risk (22,23). Failure to account for these factors may result in a spurious association between physical activity and the risk of colorectal cancer. However, both cohort studies in the present review showed a strong, inverse association between physical activity and colon cancer in men even after adjustment of potentially important risk or protective factors of colorectal cancer. Fifthly, cohort studies possess their constitutional drawbacks. For one, physical activity level assessed in a prospective cohort design would be non-differentially misclassified, leading to a dilution of association. Furthermore, only baseline measurement of physical activity was used as an exposure variable in the two Japanese cohort studies, but physical activity level may change over the life course. Finally, as with any review based on published articles, we cannot rule out a possibility of publication bias, which would work to produce spurious association even in the case of no association. However, the effect of such bias may not largely distort our conclusion because most case–control studies in this review reported results not only for physical activity but also for other lifestyle factors within the same paper or in other independent ones.

A protective association between physical activity and colorectal cancer is supported by a number of biologic mechanisms. Main hypothesized mechanisms include

Table 2. Physical activity and colorectal cancer risk, case–control study among Japanese populations

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
Kato et al. (16)	1979–87	Registry based (Aichi Cancer Registry)	Cases: histologically confirmed (90%); controls: patients with other sites of cancer excluding known alcohol-related cancers (mouth, pharynx, esophagus, liver and unknown sites)	Colon		Occupational activity			Adjusted for age	Each occupation was classified according to the proportion of physically active time on the job
				1716 men	16 600 men	High	1.00			
						Moderate	1.79 (1.50–2.15)			
						Low	1.87 (1.58–2.23)	NA		
				Proximal colon						
				445 men	16 600 men	High	1.00			
						Moderate	1.76 (1.24–2.48)			
						Low	1.92 (1.38–2.67)	NA		
				Distal colon						
				756 men	16 600 men	High	1.00			
						Moderate	1.70 (1.33–2.19)			
						Low	1.52 (1.19–1.94)	NA		
				Rectum						
				1611 men	16 600 men	High	1.00			
						Moderate	1.30 (1.10–1.55)			
						Low	1.38 (1.17–1.62)	NA		
Kato et al. (17)	1986–90	Hospital based (Aichi Cancer Center Hospital)	Cases: histologically confirmed cases among examinees of colonoscopy at the hospital; controls: population controls selected through the telephone directories	Colon		Sports activity			Adjusted for residence, sex and age (5-year age group)	*Common controls for cases of cancer of the colon and rectum
				132 (M: 79, F: 53)	578 (M: 377, F: 201)*	Almost no activity	1.00			
						<1/week	0.72 (0.44–1.19)			
						≥1/week	0.55 (0.33–0.89)			
						Occupational activity				
						Sedentary	1.00			
						Moderate	0.58 (0.37–0.90)			
						High	0.51 (0.30–0.87)			
				Rectum		Sports activity				

Continued

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
				91 (M: 60, F: 31)	578 (M: 377, F: 201)*	Almost no activity	1.00			
						<1/week	0.86 (0.50–1.50)			
						≥1/week	0.54 (0.30–0.97)			
						Occupational activity				
						Sedentary	1.00			
						Moderate	1.24 (0.72–2.15)			
						High	0.70 (0.36–1.38)			
Kotake et al. (18)	1992–94	Hospital based (10 hospitals in Kanto region)	Cases: histologically confirmed cases; controls: screening controls and hospital controls, including cancer patients	Colon		Occupational physical activity			Matched for sex, age (5-year age group)	Risk estimates for intermediate categories are not shown.
				187 (M: 111, F: 76)	187 (M: 111, F: 76)	Very active	1.0			
						Sedentary	1.1 (0.30–2.84)			
						Physical exercise				
						Often	1.0			
						Seldom	0.9 (0.17–1.89)			
				Rectum		Occupational physical activity				
				176 (M: 103, F: 73)	176 (M: 103, F: 73)	Very active	1.0			
						Sedentary	1.9 (0.66–5.54)			
						Physical exercise				
						Often	1.0			
						Seldom	1.0 (0.25–8.01)			
Inoue et al. (19)	1988–92	Hospital based (Aichi Cancer Center Hospital)	Cases: histologically confirmed cases; controls: first-visit outpatients free from cancer	Proximal colon		Physical exercise			Adjusted for age	*Common controls for cases of cancer of the colon and rectum
				51 men	8621 men*	≤4/month	1.0			
						>4/month	0.7 (0.4–1.5)			
				43 women	23 161 women*	≤4/month	1.0			
						>4/month	0.5 (0.2–1.5)			
				Distal colon						
				75 men	8621 men*	≤4/month	1.0			
						>4/month	0.7 (0.4–1.3)			
				62 women	23 161 women*	≤4/month	1.0			
						>4/month	1.0 (0.5–2.0)			
				Rectum						
				131 men	8621 men*	≤4/month	1.0			
						>4/month	0.8 (0.5–1.3)			
				70 women	23 161 women*	≤4/month	1.0			
						>4/month	0.7 (0.3–1.4)			

Ping et al. (20)	1986–94	Health checkup based (Tokai University Hospital: health checkup examinees)	Cases: histologically confirmed cases; controls: cancer-free examinees	Colorectum		Exercise			Matched (1:3) for sex, age (±2 years), data of health checking(±3 months) and residence; 35 controls were excluded due to a lack of lifestyle data	The definition of 'lack of exercise' is not stated.
				100 (M: 77, F: 23)	265 (NA)	Not lacking	1.00			
						Lacking	1.39 (0.87–2.20)			
Isomura et al. (21)	2000–03	Hospital based (two university hospitals and six affiliated hospitals	Cases: patients undergoing surgery for a first diagnosis of colorectal cancer; controls: population controls selected using two-stage random sampling method	Colon		Job-related physical activity			The number of control candidates by sex and 10-year age class were determined a priori in accordance with sex and age-specific numbers of incident cases of colorectal cancer in the Osaka Cancer Registry; Adjusted for age, smoking, alcohol use, residence, BMI and non-job physical activities or job-related physical activities	
				248 men	470 men	Sedentary	1.0			
						Moderate	0.9 (0.6–1.4)			
						Hard	0.7 (0.4–1.0)	0.06		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.9 (0.6–1.4)			
						16.0+	0.8 (0.5–1.2)	0.22		
				190 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	0.7 (0.4–1.2)	0.18		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.9 (0.5–1.5)			
						16.0+	0.8 (0.5–1.4)	0.45		
				Proximal colon		Job-related physical activity				
				88 men	470 men	Sedentary	1.0			
						Moderate	1.2 (0.6–2.2)			
						Hard	0.7 (0.4–1.4)	0.45		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	1.2 (0.6–2.1)			
						16.0+	0.9 (0.5–1.7)	0.69		

Continued

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls					
				87 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	1.2 (0.6–2.3)	0.65		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	1.5 (0.7–3.3)			
						16.0+	1.6 (0.7–3.6)	0.41		
				Distal colon		Job-related physical activity				
				159 men	470 men	Sedentary	1.0			
						Moderate	0.8 (0.4–1.4)			
						Hard	0.6 (0.4–1.0)	0.047		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.8 (0.5–1.3)			
						16.0+	0.7 (0.4–1.1)	0.19		
				103 women	297 women	Job-related physical activity				
						Sedentary	1.0			
						Active	0.4 (0.2–0.8)	0.02		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.7 (0.4–1.3)			
						16.0+	0.6 (0.3–1.1)	0.12		
				Rectum		Job-related physical activity				
				208 men	470 men	Sedentary	1.0			
						Moderate	0.9 (0.5–1.4)			
						Hard	0.6 (0.4–0.9)	0.02		
						Non-job physical activity				
						0	1.0			
						0.1–15.9	0.6 (0.4–0.9)			
						16.0+	0.5 (0.3–0.8)	0.01		

132 women	297 women	Job-related physical activity		
		Sedentary	1.0	
		Active	1.1 (0.6–1.9)	0.81
		Non-job physical activity		
		0	1.0	
		0.1–15.9	1.2 (0.7–2.3)	
		16.0+	0.9 (0.5–1.8)	0.47

NA, not available; NS, not significant; M, men; F, women.

prevention of obesity, a strong predictor of colorectal cancer, decreased inflammation, reduced levels of insulin and insulin-like growth factor 1 and modulated immune response (7,24,25). In addition, physical activity has been associated with an increased level of circulating vitamin D (26), which has an anti-carcinogenic effect on colonic epithelial cells (27) and has been related to lower risk of colon cancer (28). Other possible mechanisms include decreased bowel transit time (29), thereby resulting in less exposure of the colon to colonic contents, bile acids and other potential carcinogens. Physical activity was also related to increased prostaglandin $F_2\alpha$ (30) and reduced prostaglandin E_2 (31); the former prevents tumor development in the colon and increases gut motility (32,33), whereas the latter reduces colonic motility and promotes the proliferation of colonic cells (32,34). Moreover, physical activity has been shown to be associated with decreased prevalence of colon adenoma (35), a precursor of colorectal cancer.

The association between physical activity and colorectal cancer in Japanese studies reviewed here is generally in agreement with that of previous reviews (6–10). A consistent dose–response relationship of physical activity to a decreased risk of colon cancer was observed in both cohort and case–control studies. Moreover, agreement exists between Japanese cohort studies (14,15) and previous reviews (6–9) on the lack of association between physical activity and risk of rectal cancer. Results of the present review support a protective role of physical activity in the prevention of colon cancer.

Unlike the protective association of physical activity with colon cancer risk consistently observed here and in previous reviews (6–10), the association with rectal cancer was mixed in our review. Consistent with previous reports (6–9), cohort studies reviewed here did not show any association between physical activity and rectal cancer, while the majority of case–control studies reported weak to moderate protective association (16–18,21) and some of the case–control studies exhibited a dose–response relationship (16,17,21). The possible disagreement regarding the association of physical activity with rectal cancer observed in cohort and case–control studies in the present review may be attributed to the difference of study design, as discussed in the methodological section above.

A point of note in the present review is that men showed a stronger protective association of physical activity with colon cancer than women in cohort studies. This observation is in line with numerous studies in other countries on this topic (6–10). We had no clear reason for such sex difference in association. One possible explanation is that men and women differ in terms of the amount, intensity and duration of physical activity engaged. It is conceivable that men tend to be engaged in more strenuous physical activity when compared with women. In addition, women are more likely to participate in housework and childcare, which are difficult to assess precisely. As a result, men may provide more accurate information about their physical activity than women. Epidemiologic evidence suggests that 30–60 min per day of moderate to vigorous intensity physical activity are necessary to reduce colon cancer risk (36).

Table 3. Summary of the association between physical activity and colorectal cancer risk, cohort study

References	Study period	Study population					Magnitude of association[a]		
		Sex	Number of subjects	Ranged age (years)	Event	Number of incident cases or deaths	Colon	Rectum	Colorectum
Lee et al. (14)	1995–02	Men	29 842	40–69	Incidence	290	↓↓↓[b,c,d]	–	↓
		Women	35 180	40–69	Incidence	196	↓[b]	↑↑	–
Takahashi et al. (15)	1990–97	Men	25 279	40–64	Incidence	166	↓↓↓[d]	–	↓↓
		Women	26 642	40–64	Incidence	94	–	–	–

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition); if the magnitude of association differs between occupational and non-occupational activities or between proximal and distal colon, strongest association is reported.
[b]Proximal colon.
[c]Occupational physical activity.
[d]Non-occupational physical activity.

Table 4. Summary of the association between physical activity and colorectal cancer risk, case–control study

Reference	Study period	Study subjects						Magnitude of association[a]		
		Sex	Age range	No. of cases			No. of controls	Colon	Rectum	Colorectum
				Colon	Rectum	Colorectum				
Kato et al. (16)	1979–87	Men	≥20 year	1716	1611	NP	16 600	↓↓[d]	↓[d]	NA
Kato et al. (17)	1986–90	Men and women	Not specified	132	91	NP	578	↓↓[d,e]	↓↓[d]	NA
Kotake et al. (18)	1992–94	Men and women	Not specified	187	176	NP	363	–	↓[d]	NA
Inoue et al. (19)	1988–92	Men	24–86 year	126	131	NP	8621	–[e]	–[e]	NA
		Women	24–88 year	105	70	NP	23 161	↓[b,e]	–[e]	NA
Ping et al. (20)	1986–94	Men and women	40–84 year	NP	NP	100	265	NA	NA	–
Isomura et al. (21)	2000–03	Men	20–74 year	248	208	NP	470	↓↓[c,d]	↓↓[d,e]	NA
		Women	20–74 year	190	132	NP	297	↓↓↓[c,d]	–	NA

NP, not provided; NA, not available; M, men; F, women.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition); if the magnitude of association differs between occupational and non-occupational activities or between proximal and distal colon, strongest association is reported.
[b]Proximal colon.
[c]Distal colon.
[d]Occupational physical activity.
[e]Non-occupational physical activity.

In conclusion, epidemiological evidence for a protective association of physical activity with colorectal cancer among the Japanese population is more consistent and stronger for colon cancer than for rectal cancer. A protective association with rectal cancer was observed in some case–control studies, but not in cohort studies.

Evaluation of Evidence on Physical Activity and Colorectal Cancer in Japanese

From the results of the present review and based on the hypothesized biological plausibility, we conclude that physical activity probably reduces the risk of colorectal cancer among the Japanese population. More specifically, the evidence for the colon is probable, whereas that for the rectum is insufficient.

Acknowledgements

The authors gratefully acknowledge the assistance of Ms Izumi Suenaga.

Funding

This study was supported by Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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Appendix

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(11)1292–1302
doi:10.1093/jjco/hyr141
Advance Access Publication 4 October 2011

Public Health Report

Cigarette Smoking and Pancreas Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence in the Japanese Population

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Received July 12, 2011; accepted August 25, 2011

Objective: Cigarette smoking has been recognized as an important risk factor for pancreas cancer, but the magnitude of the association may vary among geographical areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and pancreas cancer in the Japanese population.

Methods: Original data were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient') and the magnitude of association ('strong', 'moderate', 'weak' or 'no association'), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer.

Results: We identified four cohort studies and three case–control studies. All cohort studies consistently showed positive associations between pancreas cancer and cigarette smoking, although statistical significance in each study is variable. Most of the cohort studies consistently showed that cigarette smoking had a dose–response relationship with pancreas cancer. One case–control study showed a strong positive association, but the rest did not show any association. Meta-analysis of seven studies indicated that a summary estimate for ever smoking relative to never smoking was 1.68 (95% confidence interval: 1.38–2.05).

Conclusions: We conclude that there is convincing evidence that cigarette smoking moderately increases the risk of pancreas cancer in the Japanese population.

Key words: systematic review – epidemiology – cigarette smoking – pancreas cancer – Japanese

BACKGROUND

An association between cigarette smoking and the risk of pancreas cancer has been consistently reported from all over the world. In the evaluation by the International Agency for Research on Cancer (IARC), tobacco smoke is classified as a Group 1 carcinogenic agent to humans causing cancer including pancreas cancer (1). Thus, cigarette smoking is one of the internationally well-established risk factors of pancreas cancer.

On the other hand, the risk of pancreas cancer by cigarette smoking might vary among geographical areas because of a large variability in the patterns of tobacco consumption across countries. Genetic differences might also influence association between smoking and pancreas cancer risk. Therefore, the magnitude of the association between cigarette smoking and pancreas cancer in the Japanese population might differ from that in other regions.

We review epidemiological studies on cigarette smoking and pancreas cancer risk among Japanese. This report is one of a series of articles by our research group (2–17), which is investigating the association between lifestyle and the major types of cancer in Japan.

METHODS

Search of Research on the Subject

The details of the evaluation method have been described elsewhere (2). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi (Japana Centra Revuo Medicina)* databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and pancreas cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichusi* database) to June 2011, including papers in press if available, were identified using the following as keywords: cigarette, smoking, pancreas, pancreas cancer, cohort, follow-up, case–control, Japan and Japanese. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in tables separately as cohort or case–control studies. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included, and incidence was also given priority in a single publication describing both incidence and mortality.

Evaluation of Strength of Association Between Cigarette Smoking and Pancreas Cancer Risk

An evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5 to 2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), 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 (symbol –), 0.67 to 1.5 (NS). When the multiple RRs were shown in the single study, we considered the largest RR. Criteria for the magnitude of association are summarized in Table 1. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (18), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (2). Convincing: evidence based on a substantial number between exposure and disease, with little or no evidence to the contrary, with a biologically plausible association. Probable: evidence based on epidemiologic studies showing fairly consistent associations, but with perceived shortcomings in the available evidence or some evidence to the contrary that precludes a more definite judgment. Possible: evidence based mainly on findings from case–control and cross-sectional studies, requiring more studies to support the tentative associations, which should also be biologically plausible. Insufficient: evidence based on findings of a few studies that are suggestive, but insufficient to establish an association, requiring more well-designed research to support the tentative associations. We assumed that biological plausibility corresponded to the judgment of the recent evaluation from the IARC (1). The final judgment is made based on the consensus of research group members.

Quantitative Evaluation of Association by Meta-analysis

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, a meta-analysis was conducted to obtain summary estimates of the

Table 1. Evaluation of the magnitude of association in the present report

Magnitude of association	Definition	Statistical significance	Symbol
Strong	RR < 0.5 or RR > 2.0	SS	↑↑↑ or ↓↓↓
Moderate	RR < 0.5 or RR > 2.0	NS	↑↑ or ↓↓
	1.5 < RR ≤ 2.0	SS	
	0.5 ≤ RR < 0.67	SS	
Weak	1.5 < RR ≤ 2.0	NS	↑ or ↓
	0.5 ≤ RR < 0.67	NS	
	0.67 ≤ RR ≤ 1.5	SS	
No association	0.67 ≤ RR ≤ 1.5	NS	—

RR, relative risk; SS, statistically significant; NS, not statistically significant.

Table 2. Cigarette smoking and pancreas cancer risk, cohort studies among Japanese population

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
Akiba and Hirayama (22)	1965–81 (17 years)	122 261 men	Population-based	Death	312 men	Never smoker	54	1.0	0.04	Age, prefecture, occupation, attained age (5-year interval), observation period (1996–69, 70–73, 74–77, 78–81)	
		142 857 women	Kagosihima			1–4 cigs/day	4	1.1 (0.3–2.7)			
		≥40 years old	Okayama			5–14 cigs/day	112	1.5 (1.1–2.1)			
			Hyogo			15–24 cigs/day	137	1.6 (1.2–2.2)			
			Osaka			25–34 cigs/day	10	1.2 (0.6–2.2)			
			Aichi			35+ cigs/day	5	1.3 (0.4–2.9)			
			Miyagi								
					232 women	Never smoker	198	1.0	0.02		
						1–4 cigs/day	2	0.6 (0.1–1.9)			
						5–14 cigs/day	28	1.9 (1.2–2.8)			
						15+ cigs/day	4	1.4 (0.4–3.4)			
Lin et al. (23)	1988–97 (10 years)	46 465 men	Population-based	Death	120 men	Never	19	1.0	Not described	Age, BMI, DM history and history of gallbladder diseases	
		64 327 women	45 areas in Japan		Ex-smoker	33	1.1 (0.6–1.9)				
		40–79 years	JACC study			Current smoker	68	1.6 (0.95–2.6)			
						Never	19	1.0	0.59		
						1–19 cigs/day	30	1.6 (0.91–2.9)			
						20–39 cigs/day	29	1.3 (0.74–2.4)			
						40+ cigs/day	7	3.3 (1.38–8.1)			
						Never	19	1.0	0.63		
						≥26 started age	8	1.5 (0.65–3.4)			
						23–25	8	1.3 (0.57–2.9)			
						20–22	38	1.7 (0.95–2.9)			
						<20	11	1.7 (0.82–3.7)			
						Never	19	1.0	0.92		
						<25 years smoking	2	1.3 (0.27–6.2)			
						25–34 years	9	2.0 (0.80–4.9)			
						35–44 years	25	1.7 (0.91–3.2)			
						45+	29	1.5 (0.81–2.7)			
						Non-smoker	19	1.0	0.53		
						<20 pack-years	9	2.0 (0.89–4.4)			