Table 2. Gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls					
Tajima and Tominaga (17)	1981–83	Hospital-based (Aichi Cancer Center)	Cases:	93	186	Green tea, times/day			Matched for age (±5 years), sex, time of interviews (±6 months)	
			Histologically confirmed cases			≥4	0.64	NS		
			Controls:			≤3	1.0			
			Patients without stomach cancer							
Kono et al. (18)	1979–82	Hospital-based (Karatsu Stomach Institute)	Cases:	139	Hospital controls: 2574	vs. hospital controls				
			Newly diagnosed as having gastric cancer at the Institute	74 men		Green tea, cups/day				
				65 women	1171 men	None or 1–4	1.0		Age, sex	
					1403 women	5–9	1.1			
						≥10	0.6	NS		
			Hospital controls:		General controls;					
			Patients without gastric cancer		278	≤9	1.0		Age, sex, smoking, oranges, fruits	
					148 men	≥10	0.5 (0.3–1.1)			
			General population controls:		130 women					
			Random sampling from the computerized file of residents			vs. general controls			General population:	
						Green tea, cups/day			Matched (1:2) for	
						None or 1–4	1.0		Sex	
						5–9	1.2		Age	
						≥10	0.4*	NS		
						≤9	1.0		Smoking, oranges, fruits	
						≥10	0.3 (0.1–0.7)†			

Continued

Table 2. *Continued*

References	Study time	Study subjects			Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls				
Inoue et al. (19)	1990–95	Hospital-based (Aichi Cancer Center)	Cases:	893	21 128	Green tea			
			Histologically diagnosed cases of gastric cancer at the Institute			Rarely	1.00	Coffee intake, black tea intake, gender, age, year and season at first hospital visit, habitual smoking, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, and beef intake	
						Occasional	1.00 (0.77–1.44)		
						Daily			
			Controls:			1–3 cups/day	0.96 (0.70–1.32)		
			Outpatients without cancer			4–6 cups/day	1.01 (0.74–1.39)		
						≥7 cups/day	0.69 (0.48–1.00)‡		

NS, not significant.
*$P < 0.05$.
†$P = 0.007$.
‡$P < 0.05$.

control studies consistently showed a weak negative association between intake of green tea and risk of gastric cancer (Table 4). Among them, when using the general population as a control setting, Kono et al. (18) observed a strong negative association between green tea intake and gastric cancer risk.

During the review process, we were aware of the difference in effect by sex. In all studies that presented the analysis for men and women separately, although not statistically significant, the point estimate of highest category of green tea intake for women was consistently lower than that for men; i.e. based on incidence data, compared with <1 cup/day, the RRs of drinking ≥5 cups/day for men and women were estimated as 1.5 and 0.8 (9) and 0.98 and 0.67 (11), respectively (Table 1). Based on mortality data, the corresponding values for men and women were estimated as 1.0 and 0.7 (<1 vs. ≥10 cups/day) (10), and 1.1 and 0.7 (less than several times per month vs. more than several times per week) (12), respectively (Table 1). These results suggest a small protective effect, if any, of green tea intake and development of gastric cancer for women. However, applying our definition of magnitudes of association, they slightly failed to reach the level of weak association (weak association for 0.5 to <0.67, not significant). The null association observed among men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite may point to an inconsistent effect on gastric cancer overall (11). However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women. Results from pooled analysis may lead to a better understanding of these unresolved issues.

In a pooled analysis of six cohort studies (9–11,13,20,21) involving total of 219 080 subjects and 3577 gastric cancer cases, the role of green tea intake and gastric cancer risk was analyzed for men and women separately, with consideration of smoking status, anatomic subsite and so on (16). As a result, a statistically significant, weakly decreased risk of gastric cancer with ≥5 cups/day of green tea intake among women was observed [hazard ratio (HR) = 0.79, 95% confidence interval (CI) 0.65–0.96], although no association was observed among men (Tables 1 and 3). When the anatomic subsite was considered among four cohort studies in which the data were routinely collected, the risk reduction among women was more prominent in the distal gastric region (HR = 0.70, range 0.50–0.96; *P* for trend = 0.04). Together with the results of the systematic review, this finding from the pooled analysis was also considered to finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese.

A difference in the effect of green tea intake by sex has also been observed for cardiovascular disease (14,22,23). The exact reason for the difference is unknown but may be explained, in part, by residual confounding effects of

smoking, phytoestrogens in tea and so on. It was suggested in some studies (9,14), but not all (16), that cigarette smoking might modify the effect of green tea. Tsubono et al. (9) observed a trend toward a positive association between green tea consumption and the risk of gastric cancer in subjects currently smoking ≥20 cigarettes/day (P for trend = 0.06), but not in other groups (P for the interaction term = 0.17). A similar interaction was suggested among studies investigating green tea intake and risk for cardiovascular disease (14). Higher rates of smoking may mask the effect of green tea consumption in men. Tea flavonoids such as kaempferol have been shown to exhibit estrogenic activity *in vitro* (24). In addition, tea contains lignan polyphenols, such as secoisolaracinol, which are considered phytoestrogenic (25). The phytoestrogens in tea might also partly account for the stronger protective effect of green tea in women than in men (26,27), although an estrogen-related protective mechanism against gastric cancer, if any, warrants further investigation.

Several aspects need to be discussed in relation to interpreting the present findings. Although cigarette smoking, which is suggested to have an interactive effect with green tea, was adjusted in most studies, *H. pylori* infection, a Group 1 carcinogen recognized by the International Agency for Research on Cancer (IARC), was not considered in any study. Based on the same origin of cohort study (10), Hoshiyama et al. (28) investigated whether green tea has any association with gastric cancer risk with considering *H. pylori* infection in a nested case–control study design within 157 incidence cases and 285 controls. They found that green tea intake had no protective effect against gastric cancer even after controlling for *H. pylori* infection. A previous nested case–control study that investigated plasma tea polyphenols and risk for gastric cancer reported that the decreased risk of gastric cancer by intake of tea polyphenols observed among women in the study remained even after adjusting for *H. pylori* infection (29). Some researchers used an animal model to report the inhibition of *H. pylori* urease by green tea extract (30) and the bactericidal effect on *H. pylori* infection by green tea catechins (31). A long-term habit of drinking green tea might lead to the elimination of *H. pylori*; if this is true, *H. pylori* may act as an intermediate rather than a confounding factor in the relationship between green tea and gastric cancer.

Discrepancies were noted in the effects of green tea on gastric cancer risk between case–control studies and cohort studies. The discrepancies were quantitatively shown from a recent meta-analysis of green tea intake and gastric cancer risk based on 13 studies from Japan and China (32). Compared with the lowest level of green tea intake, the RR of gastric cancer for the highest level of green tea intake was 0.73 (95% CI 0.64–0.83) for case–control studies, whereas no association was observed for cohort studies (RR = 1.04, 95% CI 0.93–1.17). The discrepancy may be partially explained by recall or selection biases that are inevitable in case–control studies. For example, it is possible that individuals with gastric cancer reduce their green tea intake due to their gastric symptoms. In fact, it has been reported that among those with gastric cancer, black tea consumption was reduced even up to 2 years before their diagnosis was made (33). Therefore, the green tea intake for gastric cancer cases among case–control studies might be partly underreported. Another point is the variation of gastric cancer mortality rates across the country. The age-adjusted gastric cancer mortality rate under age 75 in 2009 in Japan was 11.8/100 000 and ranged from 6.3 (Okinawa prefecture) to 15.7 (Akita prefecture) (34). It is interesting that gastric cancer mortality rates in the two prefectures in the case–control studies are higher than the average level, whereas the situation for cohort studies is mixed. On the basis of wide variation in gastric cancer mortality rates by area, the approach such as pooled analysis might be important.

However, the null results in cohort studies also contradict the results of previous experimental studies that suggested the protective effect of tea polyphenols on gastric cancer using *in vivo* animal models and *in vitro* cancer cell lines (3). In most of the cohort studies where the validity of green tea intake was examined, a moderate validity was shown; the Spearman coefficient for the correlation between the green tea intake according to the questionnaire and the amounts consumed according to the food records ranged from 0.29 to 0.71 (9–11,13,14). However, in all epidemiologic studies investigating green tea intake and gastric cancer risk, green tea consumption was determined only in terms of self-reported frequency of drinking, and the size of the cup was not ascertained. Furthermore, the amount of tea polyphenols in one cup varies according to preparation, i.e. the type and amount of green tea leaves, the frequency of renewing a tea batch in the pot, the temperature of boiled water or time to brew the tea and so on. A number of studies have found that hot drinks have an effect on the risk for esophageal cancer (35). Yu et al. (36) also showed that boiling hot tea had a non-significant increased risk of causing gastric cancer (odds ratio = 1.18). The risk estimates for the cardia, pylori and antrum sites regarding boiling hot tea were 2.09, 0.56 and 0.82, respectively. Furthermore, the term 'green tea' might be ambiguous because some participants may include only 'sencha', which looks green, or others may also include 'bancha/houjicha/genmaicha', which is also a commonly consumed Japanese tea but looks brown. Sencha, one of the most popular green teas in Japan, contains higher levels of tannin, vitamin C and folate than bancha/houjicha/genmaicha (37). Inaccurate measurement of green tea consumption in epidemiologic studies necessarily attenuates the small effect of green tea. It is interesting that both studies using biomarkers of green tea intake showed a statistically significant association with gastric cancer. Sun et al. (38) reported that urinary (−)-epigallocatechin (EGC) showed a statistically significant inverse association with gastric cancer. In a case–control study nested within a cohort study (11), a high plasma level of EGC was associated with an increased risk of gastric cancer in men, whereas a high plasma level of

Table 3. Summary of associations between gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References			Study period	Study subjects					Strength of association
Author	Year	Ref. no.		Sex	No. of subjects	Age range	Event	No. of cases	
Nakachi et al.	2000	8	1986–99	Men and women	8552	40+	Death	140	–
Tsubono et al.	2001	9	1984–92	Men	11 902	40+	Incidence	296	↑
				Women	14 409			123	–
Hoshiyama et al.	2002	10	1988–97	Men	30 370	40–79	Death	240	–
				Women	42 481			119	–
Sasazuki et al.	2004	11	1990–2001	Men	34 832	40–59	Incidence	665	–
				Women	38 111			227	– (distal ↓↓)
Khan et al.	2004	12	1984–2002	Men	1524	40+	Death	36	–
				Women	1634			15	–
Sauvaget et al.	2005	13	1980–99	Men and women	38 576	34–98	Incidence	1270	–
Kuriyama et al.	2006	14	1995–2001	Men	19 060	40–79	Death	138	–
				Women	21 470			55	–
Suzuki et al.	2009	15	1999–2006	Men and women	12 251	65–84	Death	68	–
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)									
Inoue et al.	2009	16	1985–2004	Men	100 479	40–103	Incidence	2495	–
				Women	118 601			1082	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

Table 4. Summary of associations between gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References			Study period	Study subjects				Strength of association
Author	Year	Ref. no.		Sex	Age range	No. of cases	No. of controls	
Tajima and Tominaga	1985	17	1981–83	Men and women	40–70	93	186	↓
Kono et al.	1988	18	1979–82	Men and women	20–75	139	Hospital 2547	↓
							General population 278	↓↓↓
Inoue et al.	1998	19	1990–95	Men and women	40+	893	21 128	↓

Explanation for each symbol is as follows when statistical significance (SS) or no statistical significance (NS), strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS).

(−)-epicatechin-3-gallate was associated with a statistically significant decreased risk of gastric cancer in women (29).

In conclusion, we found no preventive effect on gastric cancer for green tea intake in cohort studies, which have fewer biases and are more persuasive than case–control studies, where risk reduction was shown. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data from six cohort studies.

EVALUATION OF EVIDENCE ON GREEN TEA CONSUMPTION AND GASTRIC CANCER RISK IN JAPANESE

From the results of the systematic review and pooled analysis of green tea intake and gastric cancer risk and on the basis of assumed biologic plausibility, we conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

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Conflict of interest statement

None declared.

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Appendix

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Public Health Report

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

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Objective: Although cigarette smoking is considered as an important risk factor for esophageal cancer, the magnitude of the association might be varied among geographic areas. Therefore, we reviewed epidemiologic studies on the association between cigarette smoking and esophageal cancer among the Japanese population.

Methods: Original articles were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented by 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 for Research on Cancer.

Results: We identified four cohort studies and 11 case–control studies. All cohort studies and eight case–control studies showed strong positive associations between esophageal cancer and cigarette smoking. All cohort studies and five case–control studies showed that cigarette smoking had dose–response relationships with esophageal cancer. Meta-analysis of 12 studies indicated that the summary estimate for ever smokers relative to never smokers was 3.01 (95% confidence interval: 2.30–3.94). Summary relative risk for current and former smokers relative to never smokers was 3.73 (2.16–6.43) and 2.21 (1.60–3.06), respectively.

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

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

BACKGROUND

Consistent positive associations between cigarette smoking and esophageal cancer were reported from all over the world. In previous comprehensive risk evaluation by the Office of Surgeon General, the risk among current smokers was up to seven or eight times higher than the risk for lifetime non-smokers (1). In the most recent evaluation by the International Agency for Research on Cancer (IARC), cigarette smoking was evaluated as Group 1: carcinogenic to humans (2,3). Thus, cigarette smoking is a well-established risk factor for esophageal cancer.

On the other hand, the risk of esophageal cancer might vary among geographic areas. In addition, the distribution of histologic subtypes differs across countries. Squamous cell carcinoma is still prevalent in Japanese population, whereas adenocarcinoma is getting prevalent in Western population (4–7). The variability in cigarette consumption or in composition of ethnicities might be the causes of the difference. Therefore, the magnitude of association between cigarette smoking and esophageal cancer among Japanese population might differ from the other regions.

We reviewed epidemiologic studies on cigarette smoking and esophageal cancer risk among Japanese. This report is one of a series of articles by our research group (8–14), which is investigating the association between lifestyle and the major types of cancer in Japan.

PATIENTS AND METHODS

Searching of Subject Researches

The details of the evaluation method have been described elsewhere (8). In brief, original articles 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 esophageal cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011, including papers in press if available, were identified using the following as keywords: cigarette, smoking, esophagus, esophageal 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 the 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.

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

The 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) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (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 manner similar to that used in the WHO/FAO Expert Consultation Report (15), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (8): 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 (2,3). 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, meta-analysis was

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.

conducted to obtain summary estimates of the association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever smokers with never smokers were included in the meta-analysis. In case the subject study reported RRs separately according to multiple smoking status or levels, we estimated summary RR for ever smokers relative to never smokers by meta-analysis within the study and the study-specific summary RR was included in the final meta-analysis. Studies without information on CIs and different reference categories were excluded from meta-analysis. General variance-based methods were used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was examined by testing the Q-statistic (16), with the model used to determine summary RR and its 95% CI, namely a random- or fixed-effect model, selected according to the significance in the Q-statistic. Publication bias was assessed by using the funnel plot and Egger's test (17). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 10 (Stata Corp. LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding 2 cohort studies (18,19) and 1 case–control study (20) due to the analysis of the overlapping datasets, we identified 4 cohort studies (21–24) (Table 2) and 11 case–control studies (25–35) (Table 3). Of these cohort studies, one (21) presented the results by sex and three (22–24) presented the results for men only. Among case–control studies, one (26) presented the results by sex, five (25,29,30,34,35) for men and women combined, three (27,28,31) for men only and two (32,33) for women only.

A summary of the magnitude of association for the cohort studies and case–control studies was shown in Tables 4 and 5, respectively. All cohort studies (21–24) and 8 of 11 case–control studies (25,26,28,29,31,33–35) showed strong positive association between cigarette smoking and esophageal cancer. Moreover, the dose–response relationships between cigarette smoking and esophageal cancer risk were shown in all cohort studies (21–24) and five case–control studies (25,28,29,33,35). Only one cohort study (21) and one case–control study (28) showed the reversal of risk after smoking cessation. The RRs for years of quitting smoking were inconsistent between two studies.

We conducted a meta-analysis to clarify the magnitude of cigarette smoking among Japanese (Figs 1 and 2). Two studies were excluded because of the different reference category (31,34). The random-effect model was selected for the meta-analysis because heterogeneity tested for Q-statistics was significant ($Q = 42.59$, $P < 0.001$). Although Egger's test for publication bias was not significant ($P = 0.148$), funnel plot showed asymmetry (Fig. 3). Ever smokers had significantly higher summary RR than never smokers (RR 3.01, 95% CI 2.30–3.94) (Fig. 1). Seven studies (22–24,27–30) showed the RR of current and former smokers compared with never smokers. Summary RR for current and former smokers were 3.73 (95% CI, 2.16–6.43) and 2.21 (1.60–3.06), respectively (Fig. 2). When we limit the analysis to cohort studies, summary RRs for ever smokers and current smokers were 2.97 (95% CI, 2.12–4.16) and 4.20 (2.83–6.23), respectively. Several studies did not adjusted alcohol consumption in their analyses; therefore, we conducted the meta-analysis only among the studies adjusted for alcohol consumption. After excluding seven studies (21,22,25,26,29,30,33) without adjustment for alcohol drinking, summary RR for ever smokers was 2.70 (95% CI, 1.64–4.45), although heterogeneity was significant ($Q = 27.16$, $P < 0.001$).

There were several potential limitations in the Japanese studies reviewed here. One methodological issue was assessment of smoking exposures. Information on cigarette consumption was investigated by questionnaire in all cohort and case–control studies. However, the different categorization of smoking exposure was used in each questionnaire (e.g. smoking status, pack years, number of cigarettes a day). In addition, different definitions of smoking status were used. For example, former smokers with a short duration of smoking cessation were sometimes classified as current smokers. These might attenuate the association between cigarette smoking and esophageal cancer risk. In contrast, recall bias might intensify the association. The magnitude of the effects by these methodological issues may be small to influence the current observation.

Meta-analysis showed that ever smokers had significantly higher risk for esophageal cancer than never smokers. The asymmetrical appearance of the funnel plot and small P value for Egger's test suggested the existence of publication bias. Thus, summary RR of 3.01 might be overestimated. As the quantitative measurement of cigarette consumption was heterogeneous across studies, we could not see the dose–response relationships. The heterogeneity across studies is likely to be due to the different cigarette consumption levels by characteristics of subjects in each study, such as birth cohort, age, sex and base population. Moreover, only a little evidence was available about smoking cessation for esophageal cancer in Japanese population. Therefore, a pooled analysis using common cigarette consumption categories is warranted.

EVALUATION OF EVIDENCE ON CIGARETTE SMOKING AND ESOPHAGEAL CANCER RISK IN JAPANESE

From these results, and on the bases of assumed biological plausibility, we conclude that there is convincing evidence that cigarette smoking strongly increases the risk of esophageal cancer in the Japanese population.

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

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
Hirayama	21	1965–81	122 261 men	Population-based	Death	438 men	Smoking status			Not described	Age	Follow-up by death certificates, residential registry, 90% confidence intervals
			142 857 women				Non-smoker		1.0			
			≥40 years old				Daily smoker		2.24 (1.72–2.91)			
							Number of cigarettes/day					
							Non-smoker		1.0			
							1–9		1.62 (1.09–2.41)			
							10–19		2.04 (1.54–2.71)			
							≥20[a]		2.69 (2.05–3.53)			
							Age at start of smoking					
							Non-smoker		1.0			
							19 or below		1.61 (1.08–2.40)			
							20 or above		2.30 (1.76–3.00)			
							Years after smoking cessation					
							Non-smoker		1.0			
							1–4		1.53 (0.70–3.38)			
							5–9		1.13 (0.35–3.64)			
							≥10		1.96 (0.88–4.38)			
						147 women	Smoking status					
							Non-smoker		1			
							Daily smoker		1.75 (1.21–2.51)			
							Number of cigarettes/day					
							Non-smoker		1			
							1–9		1.74 (1.04–2.91)			
							10–19[a]		2.45 (1.53–3.93)			
							≥20		NA			
							Age at start of smoking					
							Non-smoker		1			
							19 or below		0			
							20 or above		1.83 (1.22–2.73)			
							Years after smoking cessation					
							Non-smoker		1			
							1–4		NA			
							5–9		NA			
							≥10		NA			

Sakata et al.	22	1988–99	46 465 men 40–79 years	Population-based 45 areas in Japan JACC study	Death	100 men	Smoking status			Not described	Adjusted for age and centers
							Non-smokers	7	1.0		
							Ex-smokers	25	2.71 (1.16–6.36)		
							Smokers	68	4.36 (2.00–9.52)		
							Age at start of smoking			0.391	
							Non-smokers	7	1.0		
							25+	13	3.85 (1.54–9.64)		
							20–24	38	4.89 (1.98–12.07)		
							10–19	13	3.24 (1.06–9.89)		
							Cigarettes smoked per day			0.431	
							Non-smokers	7	1.0		
							1–10 cigarettes/day	15	5.11 (2.07–12.65)		
							11–20 cigarettes/day	39	4.42 (1.97–9.92)		
							21–30 cigarettes/day	8	3.19 (1.11–9.19)		
							≥30 cigarettes/day	5	4.33 (1.25–14.99)		
							Years of smoking			0.014	
							Non-smokers	7	1.0		
							≤25.0	4	2.05 (0.42–9.98)		
							25.1–35.0	13	3.54 (1.27–9.89)		
							35.1–45.0[a]	32	5.34 (2.32–12.30)		
							≥45.1	15	4.85 (1.62–14.53)		
							Cumulative amount of smoking			0.086	
							Non-smokers	7	1.0		
							1–19.9 PYs	6	3.24 (1.06–9.89)		
							20.0–29.9 PYs	16	4.89 (1.98–12.07)		
							30.0–39.9 PYs	14	3.85 (1.54–9.64)		
							≥40.0 PYs	28	4.86 (2.11–11.21)		
Ishikawa et al.	23	Cohort 1 1984–92 Cohort 2 1990–97	Cohort 1 9008 men ≥40 years old Cohort 2 17 715 men 40–64 years	Population-based Miyagi pref.	Incidence	Cohort 1 38 cases Cohort 2 40 cases	Cohort 1 Category of smoking			0.008	Adjusted for age, alcohol drinking, green tea, coffee and black tea
							Never	2	1.0		
							Former	6	2.49 (0.50–12.44)		
							1–19 cigarettes/day	11	5.39 (1.18–24.61)		
							≥20 cigarettes/day	19	5.48 (1.24–24.18)		
							Cohort 2				
							Category of smoking			0.006	
							Never	2	1.0		
							Former	5	1.72 (0.33–8.92)		
							1–19 cigarettes/day	10	4.63 (1.01–21.30)		
							≥20 cigarettes/day	23	4.73 (1.10–20.34)		

Continued

Table 2. *Continued*

Author	Reference	Study period	Study population									
			Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
							Pooled 1 and 2					
							Category of smoking			0.0001		
							Never	4	1.0			
							Former	11	2.07 (0.66–6.57)			
							1–19 cigarettes/day	21	5.00 (1.70–14.66)			
							≥20 cigarettes/day[a]	42	5.09 (1.80–14.40)			
Ishiguro et al.	24	Cohort 1 1990–2004 Cohort 2 1993–2004	Cohort 1 + 2 60 876 men ≥40 years old	Population-based JPHC	Incidence	Cohort 1 + 2 215 cases	Cohort 1 + 2 Smoking status				Adjusted for age, area, BMI, preference of hot foods and drinks, ethanol consumption and flushing response	
							Never	14	1			
							Past	61	3.27 (1.78–5.99)			
							Current	140	3.69 (2.07–6.58)			
							Pack-years			0.001		
							<20	26	2.07 (1.07–4.00)			
							20–29	34	2.71 (1.44–5.11)			
							30–39	45	2.97 (1.61–5.48)			
							≥40[a]	95	4.81 (2.72–8.53)			
							Cigarettes/day among current smoker			0.001		
							<20	35	2.77 (1.43–5.34)			
							20–39	87	4.00 (2.21–7.22)			
							≥40	18	4.76 (2.31–9.81)			

NA, not available.
[a]Categories from which the magnitude of association was judged.

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		Not described	Matched for age, sex and neighborhood Not adjusted	
							Never	1.0			
							<400 000 cigarettes	1.142 (0.685–1.904)			
							≥400 000 cigarettes[a]	2.521 (1.230–5.166)			
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		Not described	Matched for age, sex, hospital and time of admission	
							Nagoya (males)				
							Non-smoker	1.0			
							Smoker[a]	5.0 (2.1–11.8)		Adjusted for age	
							Nagoya (females)				
							Non-smoker	1.0			
							Smoker	0.9 (0.3–2.6)			
							Wakayama (males)				
							Non-smoker	1.0			
							Smoker	4.3 (1.7–11.3)			
							Wakayama (females)				
							Non-smoker	1.0			
							Smoker[a]	2.3 (0.8–6.8)			
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		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
							Never smoked	1.0			
							Ex/light smoker	1.24 (0.59–2.63)			
							Moderate smoker	1.41 (0.62–3.9)			
							Moderate-to-heavy smoker[a]	1.52 (0.77–3.01)			
							Heavy smoker	1.03 (0.49–2.16)			
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		Not described	Not matched Adjusted for age, season of visit, drinking and consumption of raw vegetables	
							Never	1.0			
							Former	1.6 (0.9–2.8)			
							Current[a]	3.5 (2.1–5.8)			
							Number of cigarettes in current smokers				
							Never	1.0			
							1–19/day	3.1 (1.8–5.5)			
							≥20/day	3.5 (2.1–5.9)			
							Years of smoking in current smokers				
							Never	1.0			
							1–29	2.2 (1.1–4.4)			
							≥30	3.6 (2.1–6.0)			
							Age when started smoking in current smokers				
							Never	1.0			
							<20 years	3.9 (2.2–6.9)			
							≥20 years	3.3 (1.9–5.5)			
							Years after quitting in former smokers				
							Never	1.0			
							1–9	2.3 (1.3–4.2)			
							≥10	1.3 (0.7–2.3)			

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[b] 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.

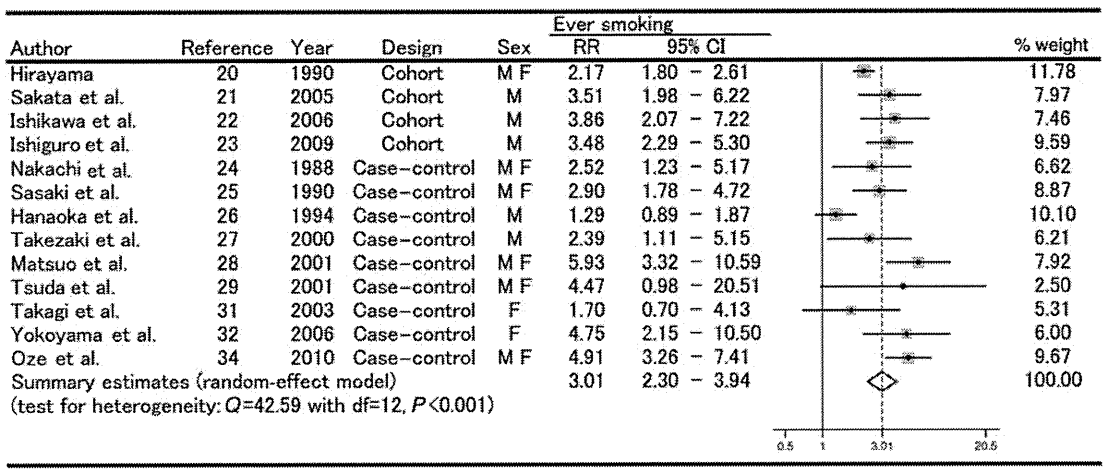

Figure 1. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

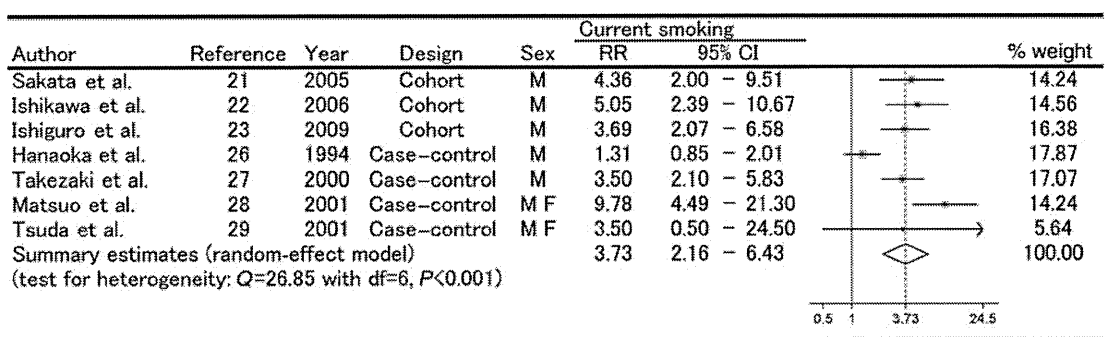

Figure 2. Summary estimates of the association between cigarette smoking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

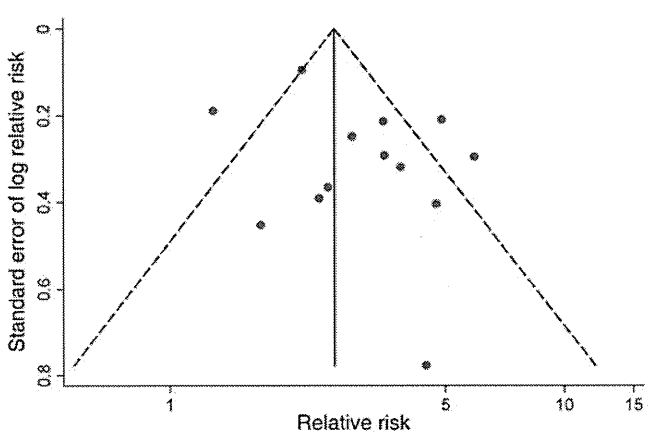

Figure 3. Funnel plot with 95% confidence limits.

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Conflict of interest statement

None declared.

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Appendix

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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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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					