						20–39	29	1.7 (0.95–3.1)		
						40–59	20	1.4 (0.73–2.6)		
						>60	7	1.7 (0.70–4.0)		
					105 women	Never	92	1.0	Not described	
						Ex-smoker	4	1.8 (0.67–5.0)		
						Current smoker	9	1.7 (0.85–3.4)		
Luo et al. (24)	Cohort 1	47 499 men	Population-based	Incidence	128 men	Never	19	1.0		
	1990–2003	52 171 women	11 public health			Former	31	1.4 (0.8–2.5)	0.01	Adjusted for age, alcohol drinking (never, occasionally, former, daily <245 g/w, daily ≥245 g/w), history of DM, BMI (14 to <21, 21 to <25, 25+), history of cholelithiasis
		Cohort 1	Centers in Japan			Current	78	1.8 (1.1–3.0)		
	Cohort 2	40–59 years				<30 pack-years	24	1.5 (0.8–2.7)		
	1993–2003	Cohort 2				≥30 pack-years	54	2.0 (1.2–3.4)		
		40–69 years								
					96 women	Never	87	1.0	Not described	
						Past	2	1.7 (0.4–7.1)		
						Current	7	2.0 (0.9–4.4)		
Nakamura et al. (25)	1992–99	14 427 men	Population-based	Death	33 men	Smoking status at baseline		Not described		Adjusted for age, body mass index, history of diabetes mellitus
		17 125 women	Takayama study			Never	4	1.00		
		≥35 years				Former	7	1.43 (0.29–7.07)		
						Current	19	3.81 (0.88–16.6)		
					33 men	Years of smoking			0.18	
						≤30	3	1.03 (0.20–5.38)		
						≥31	16	2.61 (0.87–7.84)		
					33 men	No. of cigarettes per day			0.40	
						≤20	6	5.25 (1.06–26.1)		
						≥21	13	3.53 (0.78–16.1)		
					19 women	Smoking status at baseline		Not described		
						Never	9	1.00		
						Former	2	1.70 (0.21–13.5)		
						Current	5	4.77 (1.58–14.4)		
					19 women	Years of smoking			0.001	
						≤20	2	2.47 (0.52–11.7)		
						≥21	3	9.49 (2.56–35.2)		
					19 women	No. of cigarettes per day			0.005	

Continued

Table 2. *Continued*

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										
						≤10	2	3.78 (0.81–17.7)		
						≥11	3	5.91 (1.56–22.4)		

BMI, body mass index; DM, diabetes mellitus.

association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever smokers with never or non-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 RRs for ever smokers relative to never or non-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 the meta-analysis. A general variance-based method was used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was examined by testing the Q-statistic (19), with the model used to determine the summary RR and its 95% CI, namely a random- or fixed-effect model, selected according to the SS of the Q-statistic. A publication bias was assessed by using a funnel plot and an Egger's test (20). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 11 (StataCorp LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding one cohort study (21) due to the analysis of the overlapping data sets, we identified four cohort studies (22–25) (Table 2) and three case–control studies (26–28) (Table 3). All the cohort studies (26–28) and one case–control study (28) presented the results by sex. The remaining two case–control studies presented the results for men and women combined (26,27).

A summary of the magnitude of association for the cohort and case–control studies is shown in Tables 4 and 5, respectively. All the cohort studies consistently showed positive association between cigarette smoking and pancreas cancer, although the significance of association varied across studies. Moreover, most of the cohort studies showed the dose–response or duration–response relationships between cigarette smoking and pancreas cancer risk in men (22,24) and in women (25). Among three case–control studies, one study showed strong association between cigarette smoking and pancreas cancer risk (26). This study demonstrated a strong association between passive smoking in youth and pancreas cancer risk. Another case–control study showed a dose–response relationship in combined analysis of males and females or analysis of males only (28), although each point estimate for smoking did not reach SS.

In a comprehensive review by World Cancer Research Fund and American Cancer Research Institute, several risk/protective factors were indicated with the levels of strength of evidence: body fatness as a convincing risk factor, folate-containing foods as a probable protective factor, and abdominal fat and adult attained height as probable risk factors (29). Status of consideration of these factors in the studies we reviewed need to be mentioned. Three out of four cohort studies that we reviewed considered anthropometric

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

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Mizuno et al. (26)	1989–90	Hospital-based Natl Cancer Ctr, Chiba Univ, Shinshu Univ, Cancer Inst Kobe Univ, Satitama Cancer Ctr, Nagasaki Univ	Cases: those diagnosed as pancreatic cancer pathologically radiographically or serologically. Controls: age, sex and institution matched controls with benign disease	124 (68 males, 56 females) (age range 40–79)	124 (68 males, 56 females) (age range 40–79)	Non-smoker	1.00	Not described	Matched for age, sex and institution. Adjusted for age and sex	
						Ex-smoker	1.22 (0.44–3.39)			
						Light smoker <13 cigs/day	4.50 (1.53–13.18)			
						Medium smoker 13–22 cigs/day	2.57 (1.0–6.51)			
						Heavy smoker 23+ cigs/day	2.56 (0.93–7.04)			
						(Passive smoking in youth +)				
						Non-smoker	1.00	Not described	Age and sex	
						Ex-smoker	1.65 (0.35–7.78)			
						Light smoker <13 cigs/day	8.86 (1.95–40.18)			
						Medium smoker 13–22 cigs/day	4.15 (1.05–16.46)			
						Heavy smoker 23+ cigs/day	3.97 (0.95–16.69)			
						(Passive smoking in youth −)				
						Non-smoker	1.00	Not described	Age and sex	
						Ex-smoker	0.94 (0.19–4.55)			
						Light smoker <13 cigs/day	1.81 (0.26–12.73)			
						Medium smoker 13–22 cigs/day	1.35 (0.30–6.14)			
						Heavy smoker 23+ cigs/day	2.28 (0.28–18.32)			
Ohba et al. (27)	1987–92	Hospital-based (Sapporo Medical University)	Cases: those diagnosed as pancreatic cancer pathologically or clinically) Controls: those randomly selected by phone matched for sex, age residence)	123 (no info for sex. Mean age 64.4 years)	246 (no info. available for sex, and age)	Smoking status		Not described	Matched for age	Description only in text

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* value for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Never	1.0		Sex and residence. No adjustment	
						Ex-smoker	1.25 (0.73–2.13)			
						Current smoker	1.28 (0.81–2.03)			
Inoue et al. (28)	1988–99	Hospital-based (Aichi Cancer Center Hospital)	Cases: first visit out-patients diagnosed as having pancreatic cancer. Controls: first visit out-patients confirmed to not to have cancer	200 (122 males, 78 females) (age: male mean 60.2, range 30–84, female 61.1, 32–85)	2000 (males 1220, females 780) (age: male mean 60.1, 32–82, female 60.8, 30–89)	Both sex		Not described	Age–sex matched. Adjusted for age, sex, family history of pancreatic cancer, past/present history of DM, regular exercise, bowel habits, raw vegetable intake and alcohol drinking	
						Never	1.0			
						Ever	0.92 (0.62–1.37)			
						Never	1.0	Not described		
						Former	0.60 (0.35–1.00)			
						Current	1.14 (0.75–1.74)			
						Never	1.0	<0.05		
						<20 cigs/day	0.99 (0.62–1.57)			
						20+ cigs/day	1.65 (0.95–2.8)			
						Never	1.0	Not described		
						20+ years started age	1.10 (0.71–1.70)			
						18–19 years	1.33 (0.63–2.79)			
						<18 years	1.61 (0.50–5.18)			
						Never	1.0	Not described		
						<20 years (duration)	0.90 (0.25–3.22)			
						20–39 years	1.34 (0.82–2.19)			
						40+ years	0.99 (0.57–1.72)			
						Never	1.0	Not described		
						<20 pack-years	0.74 (0.33–1.64)			
						20–39 pack-years	1.22 (0.71–2.10)			
						40+ pack-years	1.30 (0.77–2.17)			
						Male		Not described		
						Never	1.0			
						Ever	0.80 (0.50–1.28)			
						Never	1.0	Not described		
						Former	0.56 (0.32–1.00)			
						Current	0.99 (0.60–1.63)			

Never	1.0	<0.05
<20 cigs/day	0.77 (0.44–1.35)	
20+ cigs/day	1.51 (0.83–2.72)	
Never	1.0	Not described
20+ years started age	0.91 (0.54–1.52)	
18–19 years	1.34 (0.62–2.92)	
<18 years	1.54 (0.47–5.08)	
Never	1.0	Not described
<20 years (duration)	1.00 (0.19–5.36)	
20–39 years	1.19 (0.67–2.12)	
40+ years	0.82 (0.44–1.54)	
Never	1.0	Not described
<20 pack-years	1.00 (0.54–1.86)	
20–39 pack-years	1.15 (0.66–2.02)	
40+ pack-years	0.57 (0.32–1.02)	
Female		Not described
Never	1.0	
Ever	1.26 (0.62–2.56)	
Never	1.0	not described
Former	0.29 (0.04–2.37)	
Current	1.77 (0.83–3.78)	
Never	1.0	Not described
<20 years (duration)	0.67 (0.82–5.45)	
20–39 years	2.10 (0.79–5.61)	
40+ years	2.47 (0.67–9.10)	
Never	1.0	Not described
<20 pack-years	1.43 (0.47–4.37)	
20–39 pack-years	2.40 (0.79–7.26)	
40+ pack-years	1.56 (0.27–9.07)	

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

References	Study period	Study population						
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths	Category	Magnitude of association
Akiba and Hirayama (22)	1965–81	Men	122 261	40 years or older	Death	312	Cigarettes/day	↑
		Women	142 857	40 years or older	Death	232	Cigarettes/day	↑
Lin et al. (23)	1988–97	Men	46 465	40–79 years	Death	120	Smoking status	↑↑
		Women	64 327	40–79 years	Death	105	Cigarettes/day	↑↑
							Years of smoking	
Luo et al. (24)	Cohort 1	Men	47 499	Cohort 1	Incidence	128	Smoking status	↑↑
	1990–2003	Women	52 171	40–59 years	Incidence	96		↑
	Cohort 2			Cohort 2				
	1993–2003			40–69 years				
Nakamura et al. (25)	1992–99	Men	14 427	35–	Death	33	Smoking status	↑↑
							Years of smoking	↑↑
							No. of cigarettes	↑↑↑
		Women	17 125	35–	Death	19	Smoking status	↑↑↑
							Years of smoking	↑↑↑
							No. of cigarettes	↑↑↑

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

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

References	Study period	Study subjects					
		Sex	Age range (years)	Number of cases	Number of controls	Category	Magnitude of association
Mizuno et al. (26)	1989–90	Men and women	40–79	124 (M: 68, F: 56)	124 (M: 68, F: 56)	Smoking status	↑↑↑
Ohba et al. (27)	1987–92	Men and women	Not specified	123 (sex not specified)	246 (sex not specified)	Smoking status	–
Inoue et al. (28)	1988–99	Men	30–84	200 (M: 122, F: 78)	2000 (M: 1220, F: 780)	Smoking status	–
		Women	32–85			Smoking status	–

↑↑↑, strong positive association; –, no association.

factors in their evaluation and they consistently showing significant association about smoking even after adjustment of. No studies considered folate consumption, and it is difficult to quantitatively judge the effect of this lack of consideration in our evaluation. This point should be addressed in a future pooled analysis which can consider folate consumption.

In addition to the narrative review, we conducted a meta-analysis to clarify the magnitude of alcohol drinking among Japanese (Fig. 1). A random-effect model was selected for the meta-analysis because heterogeneity tested by the Q-statistic was significant ($Q = 1.322$, $P = 0.04$). Egger's test to evaluate publication bias was not significant ($P = 0.229$). Ever smokers had a significantly higher risk than never smokers (RR 1.68, 95% CI: 1.38–2.05). This result was consistently observed when we limit studies to only cohort studies (RR 1.79, 13.9–2.30). Smoking often confounds with sex and smoking was adjusted in all the studies. Sex-stratified analysis with data available (22–25,28) showed consistent association in men (1.57, 1.30–1.89) and women (1.83, 1.35–2.48). The review by IARC did not report a quantitative summary of association; however, summary statistics in this study are within the range of reported RRs in the reviewed studies (1). This might suggest that an impact of smoking on pancreas cancer risk in the Japanese population is similar to that in other populations.

There were several potential limitations in the Japanese studies in this systematic review. One methodological issue

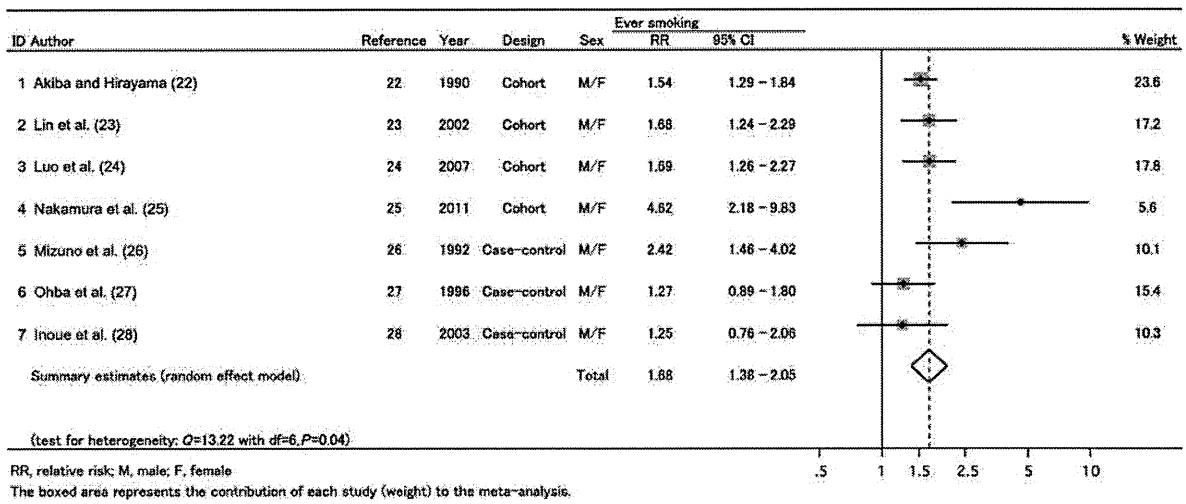

Figure 1. Summary estimates of the association between cigarette smoking and pancreas cancer risk. RR, relative risk; CI, confidence interval; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

was assessment of smoking exposures, which was investigated by a questionnaire in all cohort and case–control studies; therefore, it is difficult to completely exclude possible misclassification. Moreover, the definition and categorization of smoking exposure were heterogeneous across studies. These might bias the measure of association between cigarette smoking and pancreas cancer risk toward the null hypothesis. Recall bias might intensify the association; however, it would be unlikely because the significant association we observed was mainly from cohort studies.

Lastly, the meta-analysis showed that ever smokers had significantly increased risk for pancreas cancer than never smokers. As the quantitative measurement of cigarette consumption was heterogeneous across studies, we could not evaluate the dose–response or frequency–response relationships within the meta-analysis. Therefore, a pooled analysis using common cigarette-smoking categories is essential to quantify a dose–response or frequency–response relationship in the Japanese population.

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

From these results, we conclude that there is convincing evidence that cigarette smoking moderately increases the risk of pancreas cancer in the Japanese population.

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Conflict of interest statement

None declared.

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Appendix

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Alcohol drinking and primary liver cancer: a pooled analysis of four Japanese cohort studies

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Because studies of the association between alcohol intake and the risk of primary liver cancer use varying cut-off points to classify alcohol intake, it is difficult to precisely quantify this association by meta-analysis of published data. Furthermore, there are limited data for women in prospective studies of the dose-specific relation of alcohol intake and the risk of primary liver cancer. We analyzed original data from 4 population-based prospective cohort studies encompassing 174,719 participants (89,863 men and 84,856 women). After adjustment for a common set of variables, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of primary liver cancer incidence according to alcohol intake. We conducted a meta-analysis of the HRs derived from each study. During 1,964,136 person-years of follow-up, 804 primary liver cancer cases (605 men and 199 women) were identified. In male drinkers, the multivariate-adjusted HRs (95% CI) for alcohol intakes of 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9 and ≥92.0 g/day, as compared to occasional drinkers, were 0.88 (0.57–1.36), 1.06 (0.70–1.62), 1.07 (0.69–1.66), 1.76 (1.08–2.87) and 1.66 (0.98–2.82), respectively (p for trend = 0.015). In women, we observed a significantly increased risk among those who drank ≥23.0 g/day, as compared to occasional drinkers (HR: 3.60; 95% CI: 1.22–10.66). This pooled analysis of data from large prospective studies in Japan indicates that avoidance of (1) heavy alcohol drinking (≥69.0 g alcohol/day) in men and (2) moderate drinking (≥23.0 g alcohol/day) in women may reduce the risk of primary liver cancer.

In 2007, the International Agency for Research on Cancer stated that alcoholic beverages are "carcinogenic to humans" (Group 1) and concluded that the occurrence of primary liver cancer was causally related to alcohol intake.[1] This conclusion was bolstered by a systematic review of epidemiologic studies of Japanese, which concluded that there was "convincing" evidence that alcohol drinking increases the risk of primary liver cancer.[2] However, several issues remain to be clarified. First, due to the use of differing cut-points for alcohol intake in previous studies, it is not possible to conduct a meta-analysis of published data to precisely quantify associations between alcohol intake and the risk of primary liver cancer. Second, evidence from prospective cohort studies of women is limited and inconsistent.[3–6] There is a high

Key words: alcohols, liver neoplasms, cohort studies, pooled analysis

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incidence of hepatocellular carcinoma (HCC) in East Asia,[7] and, in Japan, HCC accounts for more than 90% of primary liver cancers.[8] Japan is unique among East Asian countries, however, because hepatitis C virus (HCV) infection is the predominant risk factor for HCC: 70% and 15% of HCCs are attributable to HCV and hepatitis B virus (HBV), respectively.[8] Indeed, the HCV-dominant pattern in Japan is similar to that of the United States,[9] where the incidence of HCC is increasing.[10] Thus, it is worthwhile to present pooled data for Japan because of the distinctive etiological characteristics of HCC in that country. To examine these issues in detail, we conducted a pooled analysis of data from 4 large-scale cohort studies performed in Japan.

Material and Methods

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan began pooling original data from major cohort studies to evaluate the association between lifestyle and major cancers in Japanese, along with systematic reviews of the relevant literature.[11] Topics for the pooled analysis were determined based on their scientific and public health importance, as determined by discussions among authors.[12,13] The following *a priori* inclusion criteria were established for the present analysis: population-based cohort studies conducted in Japan, study initiation between the mid-1980s and mid-1990s, inclusion of more than 30,000 participants, baseline collection of information on diet and amount of alcohol intake (g/day) using a validated questionnaire or similar method and collection of incidence data for primary liver cancer during the follow-up period. We identified three ongoing studies that met these criteria: (1) The Japan Public Health Center-based prospective Study (JPHC),[14] (2) The Japan Collaborative Cohort Study (JACC)[15] and (3) The Miyagi Cohort Study (MIYAGI).[16] The JPHC was treated as 2 independent studies (JPHC I and JPHC II) due to the use of different dietary questionnaires. Thus, data from a total of 4 studies were analyzed. We excluded participants with a history of cancer at baseline or missing information on alcohol intake. Selected characteristics of these studies are summarized in Table 1.

Findings regarding the association between alcohol intake and primary liver cancer risk in each cohort have been reported.[5,17–19] In this analysis, we used updated datasets, with longer follow-up periods, for the JPHC and MIYAGI. For the JACC, we updated the datasets using incidence data for primary liver cancer because previous reports on the current topic analyzed primary liver cancer mortality only.[5,18] Each study obtained approval from the relevant institutional ethical review boards, namely, those of the National Cancer Center (JPHC I and JPHC II), Nagoya University (JACC) and Tohoku University Graduate School of Medicine (MIYAGI).

Exposure assessment

In each study, alcohol drinking status was assessed by using self-administered questionnaires at baseline. Although the wording of the questions varied among studies, each study calculated alcohol intake in grams of ethanol/day as a continuous measure for regular drinkers. Because there were no data on the beverage-specific frequency of alcohol consumption, alcohol intake was calculated by multiplying average frequency by total alcohol intake from each type of beverage on a single occasion. In Japan, the *go* is the most commonly used unit for measuring the amount of alcohol intake; 1 *go* of *sake* (rice wine) is equivalent to 180 ml and contains approximately 23 g of ethanol.

Participants in JPHC I were asked about the average frequency, using six categories (<1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week and daily). Participants consuming alcoholic beverages at least once a week were also asked to identify the type and average intake of each beverage consumed. Participants in JPHC II were asked about drinking status, i.e., never-, ex-, or current drinking. Ex- and current drinkers provided information on average frequency, using four categories (1–3 days/month, 1–2 days/week, 3–4 days/week and almost daily), beverage type and average intake of each beverage type. For JPHC I and JPHC II, the amount of ethanol in each type of beverage was calculated as follows: 1 *go* of *sake* equals 23 g ethanol, 1 *go* of *shochu* or *awamori* (white spirits) equals 36 g, 633 ml of beer equals 23 g, 30 ml of whiskey or brandy equals 10 g and 60 ml of wine equals 6 g. The questionnaires in JACC and MIYAGI assessed alcohol consumption by first asking if the participant was a never-, ex-, or current drinker. Current drinkers were then asked about average frequency of drinking, using four categories (<once/week, 1–2 days/week, 3–4 days/week and almost daily), the beverage usually consumed and the amount consumed on one occasion. The total amount consumed on one occasion was converted by respondents into the corresponding *go* equivalent of sake. The questionnaires included information on the amount of each alcoholic beverage that contained the same quantity of ethanol as 1 *go* of sake and the participants were asked to refer to this guide when recording the total amount consumed on a single occasion: the alcohol content of 1 *go* of *sake* equals that of approximately 663 ml of beer, 1 *go* of wine, 1.5 *go* of *shochu*, or 2 measures of spirits.

Intake was divided into categories by using identical cutpoints across the studies. The categories were nondrinkers (never- and ex-drinker), occasional drinkers (<once/week) and regular drinkers (≥once/week: 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9, or ≥92.0 g/day for men; 0.1–22.9 or ≥23.0 g/day for women). Correlation coefficients between alcohol intakes estimated from the questionnaire and those from dietary records were 0.77 in men and 0.55 in women for the JPHC[20] and 0.77 in men and 0.71 in women for the MIYAGI.[21] The JACC, for which information on the

Table 1. Characteristics of cohort studies included in pooled analysis

Study	Population	Age range at baseline, y	Year of baseline survey	Population size	Response rate (%) for baseline questionnaire (%)	Method of follow-up	Present pooled analysis							
							Age range, y	Last Follow-up	Mean follow-up period, y	Outcome	Size of cohort		No. of cancer cases	
											Men	Women	Men	Women
JPHC I	Japanese residents of five public health-center areas in Japan	40–59	1990	61,595	82%	Cancer registry and death certificate	40–59	2004	13.6	Incidence	19,847	21,526	95	31
JPHC II	Japanese residents of 6 public health-center areas in Japan	40–69	1993–1994	78,825	80%	Cancer registry and death certificate	40–69	2004	10.5	Incidence	27,565	31,786	263	85
JACC	Residents of 45 areas throughout Japan	40–79	1988–1990	110,792	83%	Cancer registry (selected areas: 22) and death certificate	40–79	2001	10.4	Incidence	21,804	31,544	156	83
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92%	Cancer registry and death certificate	40–64	2001	11.0	Incidence	20,647	18,385[1]	91	19[1]
Total											89,863	84,856	605	199

Abbreviations: JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.
[1]Not included in main analysis.

validation of alcohol intake was not available, used the same questions on alcohol intake as the MIYAGI.

The baseline questionnaires also asked about smoking status, history of diabetes mellitus and coffee intake. Information on history of liver disease was obtained using the question, "Has a doctor ever told you that you have any of the following diseases: chronic hepatitis/liver cirrhosis (yes/no)?" on the JPHC I and JPHC II and the question, "Have you ever had any of the following diseases: liver disease (hepatitis, etc.)?" on the JACC and MIYAGI. A history of liver disease was defined as a positive response to these questions.

Case ascertainment

Participants were followed from the baseline survey (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, MIYAGI: 1990) until the final date of follow-up for incidence in each study (JPHC I: 2004, JPHC II: 2004, JACC: 2001, MIYAGI: 2001). In each study, residence status, including survival, was confirmed by examining the residential registry. Information on cancer diagnosis was collected for the entire population in the JPHC I, JPHC II and MIYAGI; cases were identified by active patient notification from major local hospitals and/or examination of population-based cancer registries. In the JACC, information on cancer diagnosis was collected in only 22 of 45 study areas. Therefore, we used data only from those areas. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[22] Each study also collected information on cause of death from death certificates and coded it according to the International Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10),[23] which was used to complement hospital and registry data on cancer diagnosis. The study outcome was defined as incidence of primary liver cancer (ICD-O-3: C22.0; ICD-10: C22.0) during the follow-up period of each study.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey for each study until the date of diagnosis of primary liver cancer, migration from the study area, death, or end of follow-up, whichever came first. Each study used Cox proportional hazards models to estimate sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) of primary liver cancer for each alcohol intake category. We assumed that occasional drinkers would have the lowest risk of primary liver cancer because never-drinkers might include participants who may have stopped drinking due to ill health and because participants who were able to drink some alcohol but nevertheless consumed the lowest amount of alcohol would have the lowest risk of primary liver cancer. We therefore used occasional drinkers as the reference category. All analyses were performed after adjustment for age at baseline (years, continuous), geographic area within the study area (for JPHC I, JPHC II and JACC), smoking status (never-smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of $\geq$20 cigarettes/day in men; never-smoker, past smoker, or current smoker in women), history of diabetes mellitus (yes or no) and coffee intake (almost never, less than one cup/day, 1 or more cups/day). The linearity assumption between age at baseline and primary liver cancer risk in each cohort was tested graphically and accepted. These covariates were selected based on previous reports.[24–26] SAS Version 9.1 (SAS Institute, Cary, NC) was used for these calculations. A random effects model, which considers both within-study and between-study variation,[27] was used to obtain a single pooled estimate of the HRs, along with standard error for the HRs, from the individual studies for each category. Study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. After exclusion of non-drinkers, the trend association was assessed in a similar manner: each study calculated the regression coefficient per 10-g increase in alcohol intake and its standard error from the Cox models, with alcohol intake in occasional drinkers defined as zero. Then, these values from individual studies were combined using a random effects model. We used Q-statistics to test for heterogeneity among studies.[27] Stata Version 9.2 (Stata Corporation, College Station, TX) statistical software was used for the simple pooled meta-analysis. All reported p-values are two-tailed.

The HRs of primary liver cancer in ex-drinkers and never drinkers are presented separately because these data were available in the JACC, MIYAGI and JPHC II. In men, we also conducted (1) an analysis stratified by history of liver disease, because previous studies indicated that the presence of chronic liver disease at baseline results in decreased alcohol consumption,[28,29] which might lead to underestimation of primary liver cancer risk[30] and (2) analyses excluding participants who received a diagnosis of liver disease in the first 3 years of follow-up. As for women, because there were no cases of primary liver cancer among occasional drinkers in the MIYAGI, we pooled data from the other 3 cohorts. To determine how this exclusion of the MIYAGI could alter the magnitude of the observed HRs, we conducted a sensitivity analysis in which we assumed one primary liver cancer case occurred in a randomly selected female occasional drinker in the MIYAGI. Then we calculated study-specific HRs and conducted the meta-analysis. We repeated this procedure 10 times. We also conducted analyses of a quadratic model that included a quadratic term for alcohol consumption (per 10 g/day) as well as a linear term. We used the Wald chi-square test to assess the statistical significance of the quadratic term.

Results

Our study included 174,719 participants (89,863 men and 84,856 women) and 804 primary liver cancer cases (605 men and 199 women) during 1,964,136 person-years of follow-up (Table 1). Approximately 50% of men habitually consumed $\geq$23.0 g/day of alcohol. In contrast, only 3% of women consumed this much alcohol per day.

Table 2. Results of pooled analysis (random effect model) of liver cancer incidence according to alcohol drinking status in men, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers, alcohol intake (g/day)					Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	23.0–45.9	46.0–68.9	69.0–91.9	≥ 92.0	HR	*p* for trend	*p* for heterogeneity
All participants										
No. of cases	228	29	82	107	76	54	29			
No. of participants	21,207	6,570	17,802	19,158	15,054	6,735	3,337			
Person-years	227,464	76,313	197,262	212,688	169,582	76,987	37,826			
Age, area-adjusted HR (95% CI)	1.69 (1.14–2.51)	1.00 (Reference)	0.88 (0.57–1.36)	1.13 (0.75–1.72)	1.16 (0.75–1.80)	1.98 (1.22–3.23)	1.91 (1.13–3.23)	1.03 (1.01–1.05)	0.006	0.294
Multivariate-adjusted HR[1] (95% CI)	1.70 (1.15–2.53)	1.00 (Reference)	0.88 (0.57–1.36)	1.06 (0.70–1.62)	1.07 (0.69–1.66)	1.76 (1.08–2.87)	1.66 (0.98–2.82)	1.02 (1.004–1.04)	0.015	0.580
Excluding cases diagnosed in first 3 years of follow-up										
No. of cases	167	18	65	85	64	45	21			
Multivariate-adjusted HR[2] (95% CI)	1.88 (1.17–3.04)	1.00 (Reference)	1.04 (0.62–1.75)	1.24 (0.75–2.05)	1.36 (0.81–2.30)	2.18 (1.24–3.86)	1.78 (0.95–3.35)	1.02 (1.01–1.04)	0.012	0.686

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II and JACC), age (continuous), history of diabetes mellitus (yes, or no), smoking status (never, past, current smoking 1-19 cigarettes/d, and ≥20 cigarettes/d), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

Table 3. Results of pooled analysis (random effect model) of liver cancer incidence according to alcohol drinking status in women, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers, alcohol intake (g/day)		Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	≥ 23.0	HR	*p* for trend	*p* for heterogeneity
No. of cases	175	7	8	9			
No. of participants	66,691	7,366	8,613	2,186			
Person-years	763,638	85,452	93,487	23,437			
Age, area-adjusted HR (95% CI)	1.50 (0.69–3.25)	1.00 (Reference)	0.88 (0.25–3.05)	4.09 (1.40–11.90)	1.17 (1.01–1.35)	0.032	0.134
Multivariate-adjusted HR[2] (95% CI)	1.50 (0.69–3.25)	1.00 (Reference)	0.86 (0.26–2.88)	3.60 (1.22–10.66)	1.11 (0.96–1.29)	0.165[3]	0.248

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II and JACC), age (continuous), history of diabetes mellitus (yes or no), smoking (never-smoker, past smoker or current smoker), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). [3]The p value for the quadratic term of alcohol intake as a continuous variable (per 10 g/day) was 0.049 and was obtained by adding the relevant variable to the model including the linear term. Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

Table 2 shows the association between alcohol intake and risk of primary liver cancer in men. We found a U-shaped association between alcohol intake and primary liver cancer risk. In male drinkers, alcohol intake was dose-dependently associated with the risk of primary liver cancer: the multivariate-adjusted HRs (95 % CI) of primary liver cancer as compared to occasional drinkers were 0.88 (0.57–1.36), 1.06 (0.70–1.62), 1.07 (0.69–1.66), 1.76 (1.08–2.87) and 1.66 (0.98–2.82) for 0.1–22.9, 23.0–45.9, 46.0–68.9, 69.0–91.9 and ≥92.0 g/day, respectively (p for trend = 0.015). The test for heterogeneity across studies was not statistically significant for the HR per 10-g/day increase in alcohol intake (p = 0.580). We found an increased risk in nondrinkers as compared to occasional drinkers (multivariate-adjusted HR: 1.70; 95% CI: 1.15–2.53). Using data from the JACC, MIYAGI and JPHC II, the multivariate-adjusted HRs in ex-drinkers and never drinkers as compared to occasional drinkers were 3.30 (2.02–5.39) and 1.32 (0.82–2.12), respectively. The results were essentially unchanged when cases diagnosed in the first 3 years of follow-up were excluded.

As for women, because there were no cases of primary liver cancer among occasional drinkers in the MIYAGI, we pooled data from the other 3 cohorts. Drinkers who consumed ≥23.0 g/day of alcohol had a significantly increased risk of primary liver cancer as compared to occasional drinkers (multivariate-adjusted HR: 3.60; 95% CI: 1.22–10.66; Table 3). The multivariate-adjusted HR per 10-g/day increase in alcohol intake in women was not statistically significant for primary liver cancer (p for trend = 0.165). We found a nonsignificant increase in risk among nondrinkers as compared to occasional drinkers (multivariate-adjusted HR: 1.50; 95% CI: 0.69, 3.25). Using data from the JACC and JPHC II, the multivariate-adjusted HRs for ex- and never drinkers as compared to occasional drinkers were 3.12 (0.85–11.38) and 1.85 (0.40–8.50), respectively.

In the sensitivity analysis for women, we assumed that one primary liver cancer case occurred in a randomly selected female occasional drinker in the MIYAGI so as to include data from that study. Then we calculated study-specific HRs and conducted the meta-analysis. We repeated this procedure 10 times. The results were essentially unchanged: the point estimates of the pooled multivariate HR of primary liver cancer were 1.43–1.45 for nondrinkers, 0.81–0.82 for an alcohol intake of 0.1–22.9 g/day and 3.72–3.78 for an alcohol intake of 23.0≥g/day.

Table 4 shows the associations of alcohol intake with primary liver cancer risk in men, after stratification by history of liver disease. In the analysis of men without a history of liver disease, the JACC was not included because there were no primary liver cancer cases among occasional drinkers. We found a positive association between alcohol intake and primary liver cancer among men without a history of liver disease (p for trend = 0.010); there was no such association among men with a history of liver disease (p for trend = 0.859). In addition, we found no increased risk among nondrinkers as compared to occasional drinkers in men without a history of liver disease. Among all the pooled multivariate-adjusted models, the p-value for the quadratic term was statistically significant only in women (p = 0.049, Table 3).

Discussion

In this pooled analysis of major population-based cohort studies carried out in Japan, occasional drinkers and those who drank <23.0 g alcohol/day had the lowest risks of primary liver cancer. There was a positive linear association with increasing alcohol intake in drinkers and approximately 70% of the excess risk of primary liver cancer was attributable to participants with an alcohol intake of ≥69.0 g per day. This positive association was pronounced in male drinkers without a history of liver disease; however, no such

Table 4. Pooled multivariate hazard ratios (random effect model) for the association between alcohol intake and liver cancer incidence by history of liver disease in men, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinker, daily alcohol intake (g/day)				Alcohol intake as a continuous variable (per 10 g/day)[1]		
			0.1–22.9	23.0–45.9	46.0–68.9	≥ 69.0	HR	*p* for trend	*p* for heterogeneity
No history of liver disease									
No. of cases	62	17	42	55	37	48			
Multivariate-adjusted HR[2] (95% CI)	1.01 (0.59–1.74)	1.00 (Reference)	0.94 (0.47–1.88)	1.17 (0.68–2.04)	1.16 (0.65–2.07)	1.96 (1.12–3.45)	1.02 (1.01–1.04)	0.010	0.490
History of liver disease									
No. of cases	135	12	31	34	26	27			
Multivariate-adjusted HR[2] (95% CI)	1.54 (0.83–2.84)	1.00 (Reference)	0.73 (0.27–1.96)	0.89 (0.40–2.00)	0.74 (0.30–1.81)	0.80 (0.38–1.67)	1.01 (0.95–1.07)	0.859	0.466

[1]Trend association was assessed after exclusion of nondrinkers. Alcohol intake in occasional drinkers was defined as zero. [2]Multivariate-adjusted HR was adjusted for geographic area (in the JPHC I, JPHC II, and JACC), age (continuous), history of diabetes mellitus (yes, or no), smoking status (never, past, current smoking 1-19 cigarettes/d, and ≥20 cigarettes/d), and coffee intake (almost never, <1 cup/day, ≥1 cup/day). Abbreviations: HR, hazard ratio; CI, confidence interval; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study.

association was found in men with a history of liver disease. In women, we also found a positive association between alcohol drinking and primary liver cancer risk in current drinkers with an alcohol intake of ≥23.0 g per day.

In addition to the carcinogenicity of acetaldehyde,[31] which is a metabolite of alcohol, several potential biologic mechanisms have been proposed to explain the effect of alcohol on hepatocarcinogenesis, including the induction of cytochrome P-450 2E1, which potentially leads to activation of procarcinogen[32] and inhibition of phase II enzymes, thus affecting the clearance of carcinogens;[33] deficiencies in various anticarcinogenic nutrients,[34] including carotenoids;[35] and aberrant DNA methylation of tumor suppressor genes and oncogenes, which might result from alterations in carbon metabolism due to alcohol intake.[36]

In women, only two prospective studies have conducted dose-specific analyses of alcohol intake and its association with primary liver cancer incidence. In Japan, Goodman et al reported an increased risk of liver cancer in women: the multivariate-adjusted relative risk of women who drank 70 ml of alcohol/week as compared to never drinkers was 2.02 (0.99–4.09).[3] In the United Kingdom, a 1.7-fold risk of liver cancer was found in women who drank ≥15 drinks/week (≥21.4 g alcohol/day) as compared to those who drank ≤2 drinks/week (2.9 g alcohol/day).[6] In our study, we also found a 3.6-fold risk in women who drank ≥23 g alcohol/day as compared to occasional drinkers (<once/week). Because of the limited number of primary liver cancer cases among female drinkers in our study and the use of different alcohol consumption categories in previous studies, it was difficult to assess relative risks among studies. However, the present and previous findings suggest that even moderate alcohol consumption in women increases the risk of primary liver cancer.

We found an increased risk of primary liver cancer in male and female nondrinkers as compared to occasional drinkers. Because the HRs in ex-drinkers are higher than those in never drinkers among both men and women, the increased risk may be due to the former. This explanation is plausible when we consider that ex-drinkers may have stopped drinking due to ill health.

In contrast to the positive association among male drinkers without a history of liver disease, there was no such association in those with a history of liver disease. Although information on liver disease was self-reported and not confirmed by medical records, it is important to consider the possibility that participants changed their drinking behavior. Self-reported information on liver disease indicates awareness of such a condition and suggests recognition of a need to reduce or quit alcohol drinking, as advised by physicians or other health care providers. Because the association among male drinkers with a history of liver disease might be distorted by a reduction in alcohol drinking, the association among participants without liver disease is likely to be a better reflection of the healthy population. The absence of an association in those with a history of liver disease is consistent with findings of

studies conducted among chronic liver disease patients (particularly patients with cirrhosis) that report no association[37,38] or, surprisingly, an inverse association.[39–41]

Our study had several strengths. First, we analyzed data from large scale population-based cohort studies that used validated questionnaires to collect data on alcohol intake. Second, each study controlled for a common set of available variables that are known or believed to cause or prevent primary liver cancer. Third, by pooling data from populations with large variations in alcohol intake, we were able to investigate risk in men with high alcohol intake and to calculate the HR of primary liver cancer in men who drank ≥92.0 g of alcohol/day. Finally, we conducted stratified analysis by history of liver disease, by which we could determine the influence of chronic liver disease on the association between alcohol drinking and primary liver cancer.

The limitations of our study warrant mention. First, we had no information on HBV and HCV infection status. If these viral infections were related to a decrease in alcohol intake, the HRs of primary liver cancer according to alcohol drinking categories would be underestimated. Nonetheless, among healthy participants, including hepatitis virus carriers who were unaware of infection, such a decrease in alcohol intake due to infection is not likely. However, underestimation might occur among participants with chronic liver disease if participants with more severe chronic liver disease tended to drink less alcohol at baseline for any reason (eg, impaired liver function or advice from a physician). Taken together, we cannot exclude the possibility of underestimation of HRs for primary liver cancer in drinkers. A second limitation is that because there were no cases of primary liver cancer among women in the reference category in the MIYAGI, we could not include data from that study in the pooled estimate. Although the number of primary liver cancer cases in the MIYAGI was small (only one and two cases for alcohol intakes of 0.1–22.9 g/day and ≥23.0 g/day, respectively), we conducted a sensitivity analysis and the results were essentially unchanged. Third, we could not obtain information on genetic polymorphisms related to alcohol-metabolizing enzymes. Approximately half of Japanese have a variant allele, aldehyde dehydrogenase 2 (*ALDH2*),[42] which is related to a high blood concentration of acetaldehyde.[43] In a case-control study conducted in Japan, Sakamoto et al suggested that the *ALDH2* polymorphism may modify HCC risk among light to moderate drinkers: the odds ratios of HCC in participants who drank <69 g of alcohol/day, as compared to nondrinkers, were 3.4 (0.9–12.2) in carriers of *ALDH2*2* and 0.8 (0.3–2.2) in noncarriers.[44] The possible interaction between alcohol intake and genetic polymorphisms related to alcohol-metabolizing enzymes on the risk of primary liver cancer requires further study.

In conclusion, this pooled analysis of data from large prospective studies in Japan indicates that avoidance of: (1) heavy alcohol drinking (≥69.0 g alcohol/day) in men and (2) moderate drinking (≥23.0 g alcohol/day) in women may reduce the risk of primary liver cancer.

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Epidemiology

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Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan

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Background: Obesity has been recognized as important risk factors for colorectal cancer. However, limited evidence is available on colorectal cancer and body mass index (BMI) in Asian population.

Methods: We conducted a pooled analysis of eight population-based prospective cohorts studies in Japan with more than 300 000 subjects to evaluate an impact of obesity in terms of BMI on colorectal cancer risk with unified

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categories. We estimated summary hazard ratio (HR) by pooling of study-specific HR for BMI categories with random effect model.

Results: We found a significant positive association between BMI and colorectal cancer risk in male and female. Adjusted HRs for 1 kg/m^2 increase were 1.03 [95% confidence interval (CI) 1.02–1.04] for males and 1.02 (95% CI 1.00–1.03) for females. The association was stronger in colon, especially in proximal colon, relative to rectum. Males showed a stronger association than females. Population attributable fraction for colorectal cancer by BMI ≥25 kg/m^2 was 3.62% (95% CI 1.91–5.30) for males and 2.62% (95% CI 0.74–4.47) for females.

Conclusions: We found significant association between BMI and colorectal cancer risk by pooling of data from cohort studies with considerable number of subjects among Japanese population. This information is important in cancer control planning, especially in Asian population.

Key words: body mass index, cohort study, colorectal cancer, Japanese, obesity, pooled analysis

introduction

A condition of overweight or obese is recognized as one of the strong risk factors on many health conditions including some cancers and more than a billion of people in the world are now in that condition [1]. As in the west, many Asian countries including Japan are experiencing a steep rise in the prevalence of obesity in their populations, although the prevalence remains lower compared with those in the Western countries [2, 3].

A higher body mass index (BMI) has been identified as an independent risk factor for colorectal cancer in many epidemiologic studies [4–11]. Recent meta-analysis including studies mainly from Western countries demonstrated moderate but significant association between BMI and colorectal, especially colon cancer risk [12–14]. Considering different trends in obesity prevalence and colorectal cancer incidence between Western and Asian countries, it is essential to have a concrete estimates of impact of BMI on colorectal cancer incidence in Asian population. A recent pooled analysis from Asian countries reported a positive association between colorectal cancer mortality and BMI [15]; however, to the best of our knowledge, scarce evidence by pooled analysis with considerable population size is available on BMI and colorectal cancer incidence in Asia.

In the present study, we conducted a pooled analysis of eight population-based prospective cohorts studies in Japan with >300 000 subjects to evaluate the impact of high BMI on colorectal cancer risk with unified BMI categories.

materials and methods

study population

The present study was conducted using data from eight representative ongoing large-scale population-based cohort studies in Japan, namely (i) the Japan Public Health Center-based Prospective Study (JPHC-I) [16], (ii) the Japan Public Health Center-based Prospective Study (JPHC-II) [16], (iii) the Japan Collaborative Cohort Study (JACC) [17], (iv) the Miyagi Cohort Study (MIYAGI-I) [18], (v) the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II) [19], (vi) the Three-Prefecture Cohort study in Aichi (AICHI) [19], (vii) the Takayama Study (TAKAYAMA) [20] and (viii) the Ohsaki Cohort Study (OHSAKI) [21]. All of these studies started after the mid-1980s and enrolled >30 000 participants. Furthermore, each included exposure information on anthropometric factors in the baseline questionnaire and collected the incidence or mortality of all cancers as outcome information during follow-up. The relevant institutional ethical review board approved each study. Five of these studies (JPHC-I and -II, JACC, MIYAGI-I and TAKAYAMA) have already published results on the association between BMI and colorectal cancer risk in the respective cohort [8, 20, 22, 23]. In this study, we reanalyzed the results of each study using the updated dataset. Selected characteristics of the cohort studies included in the present study are described in Table 1.

follow-up

Subjects were followed from the baseline survey (JPHC-I and -II: 1990–1994, JACC: 1988, MIYAGI-I: 1990, Miyagi-II: 1984, AICHI: 1958, TAKAYAMA: 1992 and OHSAKI: 1994) until the last date of follow-up in each study (JPHC-I and -II: 2006, JACC: 2001, MIYAGI-I: 2003, MIYAGI-II: 1992, AICHI: 2000, TAKAYAMA: 1999 and OHSAKI: 2003). Residence status in each study, including survival, was confirmed through the residential registry. Information on the cause of death was obtained from death certificates, coded according to the International Classification of Disease, Tenth Revision (ICD-10) [24]. Information on cancer diagnosis was collected for the whole population and was coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [25].

assessment of outcome

Study outcome was defined as the incidence of colorectal cancer (ICD-O-3 T-code: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9 and C20.9) during the follow-up period of each study. Subjects were categorized for subsite analysis as follows: (i) colorectal cancer overall: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9 and C20.9, (ii) colon cancer: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8 and C18.9, (iii) proximal colon cancer: C18.0, C18.1, C18.2, C18.3 and C18.4, (iv) distal colon cancer: C18.5, C18.6 and C18.7 and (v) rectal cancer C19.9 and C20.9.

assessment of exposure

BMI was assessed by self-administered questionnaires at baseline in each study. Although the style of the questions differed by study, each study calculated BMI as weight in kilogram divided by square of the height in meter in their questionnaires. BMI was then divided into categories by using identical cut points across studies: <19, 19 to <21, 21 to <23, 23 to <25, 25 to <27, 27 to <30 and ≥30 kg/m^2. We defined 23 to <25 kg/m^2 as reference category. Correlation coefficients that compared BMI estimated from the questionnaire with BMI from actually measured weight and height were JPHC-I and -II: 0.89 in men and 0.90 in women [26] and MIYAGI-I 0.91 for both sexes [5]. Correlation coefficients for height and weight in both sexes in TAKAYAMA were 0.93 and 0.97 [20] and in MIYAGI-I 0.97

Table 1. Characteristics of the eight cohort studies in the pooled analysis of the association between body mass index and colorectal cancer incidence

Study	Population	Age range at baseline, years	Year of baseline survey	Population size	Response rate (%) of the baseline questionnaire	Method of follow-up	For the present pooled analysis							
							Age range, years	Last follow-up time	Mean follow-up period, years	Outcome	Size of the cohort		Number of cancer cases	
											Men	Women	Men	Women
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61 595	82	Cancer registry and death certificate	40–59	2006	16.1	Incidence	20 191	21 686	546	320
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78 825	80	Cancer registry and death certificate	40–69	2006	12.8	Incidence	28 928	32 015	619	370
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110 792	83	Cancer registry (selected areas: 22) and death certificate	40–79	2001	10.3	Incidence	24 513	35 483	487	345
MIYAGI-I	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47 605	92	Cancer registry and death certificate	40–64	2003	12.7	Incidence	21 109	22 685	420	270
MIYAGI-II	Residents of 3 municipalities in Miyagi Prefecture, Japan	40+	1984	31 345	94	Cancer registry and death certificate	40+	1992	7.6	Incidence	13 010	15 944	164	122
AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33 529	90	Cancer registry and death certificate	40–103	2000	11.5	Incidence	15 253	16 895	196	146
TAKAYAMA	Residents of Takayama city, Gifu Prefecture, Japan	35+	1992	31 552	85	Colonoscopy data at two main hospitals	35+	1999	6.9	Incidence	13 392	15 537	149	113
OHSAKI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	52 029	95	Cancer registry and death certificate	40–79	2003	7.7	Incidence	21 531	23 212	474	238
Total				447 272							157 927	183 457	3055	1924

JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study.

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