and 0.85 [5], respectively. JACC and OHSAKI, for which information on the validation of BMI was not available, utilized the same questions on weight and height as MIYAGI-I. For MIYAGI-II and AICHI, there has been no information on the validation of BMI; the question was similar to JPHC-I and -II.

statistical analysis

Person-years of follow-up were calculated from the date of baseline survey in each study until the date of diagnosis of any cancer. To be pooled in estimation of summary statistics, we conducted study-specific analysis. Each analysis was stratified by sex. For females, we further stratified the analysis by menopausal status. Each analysis used a Cox proportional hazards model to estimate the hazard ratios (HR) and their two-sided 95% confidence intervals (CI) of colorectal cancer by each BMI category. All studies carried out two models in the estimation of HRs, model 1: age (and area within each study for JPHC and JACC)-adjusted HRs and model 2: smoking and drinking in addition to model 1. In model 2, smoking for male was categorized into never smoker, former smoker, current smoker with <20 cigarettes/day, current smoker with ≥20 pieces/day or missing and that for female was categorized into never smoker, former smoker, current smoker and missing. Drinking for male was categorized into nondrinker, occasional drinker (less than once a week) and current drinker (<23, 23 to <46, 46 to <69, 69 to <92 and ≥92 ethanol g/day) and that for female was nondrinker, occasional drinker and current drinker (<23 and ≥23 ethanol g/day). For six of the eight cohort studies, we adjusted other potential confounders (model 3). Model 3 included total energy (kilocalories per day), red meat (grams per day), dietary fiber (grams per day), calcium (milligrams per day), folate (micrograms per day) consumption in quartile in each study and recreational physical activity (JPHC-I and -II: almost everyday or not and JACC, MIYAGI-I and OHSAKI: ≥5 h/day or not). All the analyses were done by SAS (Version 9.1; SAS Institute, Inc., Cary, NC) or STATA (Version 10.1; Stata Corporation, College Station, TX) statistical software was used for estimations.

To obtain a single pooled estimate of the HR from the individual studies for each category, we applied a random effects model [27]. We did not include in the study any pooled estimates for categories without cases. The extent of heterogeneity for each category was indicated by Cochran's Q-statistic, which was considered statistically significant when $P < 0.10$. The I^2-statistic was also reported to describe the percentage of total variation in the study-specific HRs, which was due to heterogeneity [28]. Dose–response relationship was examined by models in which actual BMI values were included as explanatory variable, which would provide HRs by 1 kg/m^2 increase of BMI. The 'metan' command (http://www.stata.com/stb/stb44) for STATA was used for meta-analysis.

In addition, to express the impact of BMI on the risk of colorectal cancer, the population attributable fraction (PAF) (%) was estimated as pd(HR−1)/HR, where pd is the proportion of cases exposed to the risk factors [29].

results

As shown in Table 1, the present pooled analysis included eight large-scale population-based prospective cohort studies comprising 341 384 subjects (157 927 males and 183 457 females) with 4979 incident colorectal cancer cases (3055 males and 1924 females) during 3 765 498 person-years of follow-up (average follow-up: 11.0 years). At baseline, those with BMI ≥25 kg/m^2 consisted 23.3% for males and 25.2% for females. These values are comparable to those reported in the same period with the same age group [2].

Table 2 shows results for male. For colorectal cancer, we observed statically significant HRs over unity for those with BMI 27–29.9 [age, area, smoking and drinking adjusted (model 2) HR (aHR) = 1.21, 95% CI 1.05–1.40] and for those with BMI ≥30 (aHR = 1.50, 95% CI 1.15–1.96). Moreover, it showed linear trend (aHR for per 1 kg/m^2 increase in BMI = 1.03, 95% CI 1.02–1.04). Similar trends were seen in other patterns of analyses for colorectal cancer. Those with BMI <25 showed aHR below unity, though they were not statistically significant. In subsite-specific analyses, we observed a consistent result in terms of linear trends except rectal cancer. For rectal cancer, only those with BMI ≥30 kg/m^2 showed significant association. Interestingly, effect of higher BMI appeared in smaller BMI values in more proximal site. Proximity of subsites seemed associated with smaller threshold of BMI. A significant association with proximal colon cancer appeared in those with BMI >25 kg/m^2, while the significant association appeared in BMI >27 kg/m^2 for distal colon cancer and BMI ≥30 kg/m^2 for rectal cancer. Significant reduced risk was not observed in leaner subgroups using overall dataset. We also evaluated potential heterogeneity of results. We found that colorectal cancer analyses showed marginally significant heterogeneity, but for subsite-specific analyses, there seemed no significant heterogeneity across studies.

Table 3 shows results for females. Although point estimates of aHRs were relatively smaller than those for males, trends of association were consistent with males. The aHRs for colorectal cancer by BMI per 1 kg/m^2 were 1.02 (95% CI 1.00–1.03). In the subsite-specific analyses, colon cancer showed positive association regardless of subsite. In contrast, rectal cancer did not show linear association at all. In distal colon cancer, significant association was seen for those with BMI 25–26.9 kg/m^2 group and ≥30 kg/m^2 groups but not with 27–29.9 kg/m^2 groups. Stratified analysis by menopausal status showed that the association was significant in colon cancers among postmenopausal women but not in premenopausal women. For rectal cancer, aHRs higher than unity were seen in those with BMI <19 kg/m^2 though not significant. We did not see any statistically significant heterogeneity in all patterns of analysis.

We observed statistically significant association between higher BMI and colorectal cancer risk in this pooled analysis. By using current results, we estimated PAF of BMI ≥25 kg/m^2 on colorectal cancer in men and women. For males, PAFs estimates were 1.56% for BMI 25–26.9 group, 1.42% for 27–29.9 group and 0.64% for 30 or higher group. As a whole, 3.62% (95% CI 1.91–5.30) was attributed to 25 or higher BMI for male colorectal cancer. For females, PAFs estimates were 0.89% for BMI 25–26.9 group, 0.91% for 27–29.9 group, 0.83% for 30 or higher group and 2.62% (95% CI 0.74–4.47) for a whole.

discussion

This study is the first and the largest pooled analysis examining an association between BMI and colorectal cancer risk among Asian population, to the best of our knowledge. By pooling data of eight population-based cohort studies with

Table 2. Pooled analysis for body mass index (BMI) and colorectal cancer risk according to subsite[d] (male)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend P	P, I^2 (%) For trend	For the highest category
Number of subjects (n =)	9512	27 136	42 789	41 648	22 875	11 436	2531				
Person-years (n =)	90 944.5	286 483.52	464 961.22	463 999.5	257 394.43	130 096.7	28 723.75				
Colorectal cancer											
Number of cases (n =)	159	501	801	805	480	250	59				
CR (per 100 000)	174.83	174.88	172.27	173.49	186.48	192.16	205.4				
HR (model 1) overall[a]	0.86 (0.72–1.02)	0.95 (0.85–1.06)	0.95 (0.86–1.05)	Reference	1.107 (0.99–1.24)	**1.20 (1.04–1.38)**	**1.47 (1.13–1.93)**	**1.03 (1.02–1.04)**	<0.001	P = 0.554, 0	P = 0.056, 51.2
HR (model 2) overall[b]	0.87 (0.73–1.03)	0.94 (0.84–1.05)	0.94 (0.86–1.04)	Reference	1.11 (0.99–1.24)	**1.21 (1.05–1.40)**	**1.50 (1.15–1.96)**	**1.03 (1.02–1.04)**	<0.001	P = 0.462, 0	P = 0.061, 50.2
HR (model 3) overall[c]	0.91 (0.74–1.12)	0.99 (0.88–1.12)	0.95 (0.85–1.06)	Reference	**1.14 (1.01–1.29)**	**1.24 (1.06–1.44)**	**1.24 (1.06–1.44)**	**1.03 (1.02–1.04)**	<0.001	P = 0.643, 0	**P = 0.010, 69.8**
HR (model 1) excluding early cases[a]	**0.80 (0.66–0.98)**	0.95 (0.83–1.07)	0.93 (0.84–1.04)	Reference	**1.13 (1.00–1.28)**	**1.22 (1.04–1.43)**	**1.57 (1.18–2.09)**	**1.04 (1.02–1.05)**	<0.001	P = 0.637, 0	P = 0.190, 31.2
HR (model 2) excluding early cases[b]	**0.81 (0.66–0.99)**	0.93 (0.82–1.05)	0.93 (0.83–1.03)	Reference	**1.13 (1.00–1.28)**	**1.23 (1.05–1.45)**	**1.59 (1.20–1.35)**	**1.04 (1.03–1.05)**	<0.001	P = 0.652, 0	P = 0.219, 27.5
HR (model 3) excluding early cases[c]	0.86 (0.68–1.09)	0.99 (0.86–1.14)	0.93 (0.83–1.05)	Reference	**1.16 (1.02–1.33)**	**1.26 (1.06–1.49)**	**1.58 (1.15–2.17)**	**1.04 (1.02–1.05)**	<0.001	P = 0.952, 0	P = 0.042, 59.5
Colon cancer											
Number of cases (n =)	98	317	473	512	319	168	32				
CR (per 100 000)	107.76	110.65	101.73	110.34	123.93	129.13	111.41				
HR (model 1) overall[a]	0.82 (0.66–1.03)	0.94 (0.82–1.08)	0.88 (0.77–1.00)	Reference	**1.16 (1.01–1.34)**	**1.28 (1.07–1.52)**	1.38 (0.96–1.98)	**1.04 (1.02–1.06)**	<0.001	P = 0.183, 16.9	P = 0.183, 32.1
HR (model 2) overall[b]	0.84 (0.67–1.04)	0.94 (0.81–1.08)	**0.86 (0.76–0.97)**	Reference	**1.16 (1.01–1.34)**	**1.27 (1.07–1.52)**	1.37 (0.96–1.98)	**1.04 (1.02–1.06)**	<0.001	P = 0.300, 16.5	P = 0.213, 28.2
HR (model 3) overall[c]	0.91 (0.70–1.17)	1.00 (0.85–1.16)	0.87 (0.75–1.00)	Reference	**1.17 (1.01–1.36)**	**1.31 (1.09–1.58)**	1.47 (0.99–2.18)	**1.04 (1.02–1.06)**	<0.001	P = 0.358, 9.1	P = 0.096, 52.7
HR (model 1) excluding early cases[a]	**0.76 (0.59–0.99)**	0.98 (0.84–1.14)	0.90 (0.77–1.02)	Reference	**1.18 (1.01–1.38)**	**1.32 (1.09–1.60)**	**1.67 (1.15–2.44)**	**1.05 (1.03–1.06)**	<0.001	P = 0.500, 0	P = 0.487, 0

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Table 2. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend P	P, I^2 (%) For trend	For the highest category
HR (model 2) excluding early cases[b]	0.77 (0.59–1.00)	0.97 (0.83–1.13)	0.88 (0.77–1.02)	Reference	**1.18 (1.01–1.38)**	**1.32 (1.09–1.60)**	**1.66 (1.14–2.43)**	**1.05 (1.03–1.07)**	<0.001	$P = 0.489$, 0	$P = 0.551$, 0
HR (model 3) excluding early cases[c]	0.81 (0.60–1.11)	1.04 (0.87–1.23)	0.88 (0.75–1.02)	Reference	**1.18 (1.00–1.39)**	**1.34 (1.09–1.65)**	**1.81 (1.20–2.72)**	**1.04 (1.02–1.06)**	<0.001	$P = 0.556$, 0	$P = 0.411$, 0
Proximal colon cancer[d]											
Number of cases (n =)	34	114	177	182	126	66	11				
CR (per 100 000)	37.39	39.79	38.07	39.22	48.95	50.73	38.3				
HR (model 1) overall[a]	0.94 (0.64–1.37)	0.98 (0.77–1.25)	0.95 (0.77–1.17)	Reference	**1.29 (1.03–1.60)**	**1.43 (1.07–1.91)**	1.57 (0.84–2.92)	1.01 (1.00–1.01)	0.053	$P = 0.794$, 0	$P = 0.891$, 0
HR (model 2) overall[b]	0.98 (0.67–1.44)	1.01 (0.79–1.28)	0.96 (0.78–1.18)	Reference	**1.29 (1.02–1.62)**	**1.42 (1.06–1.89)**	1.55 (0.83–2.88)	**1.04 (1.01–1.06)**	0.011	$P = 0.639$, 0	$P = 0.931$, 0
HR (model 3) overall[c]	0.98 (0.64–1.51)	1.08 (0.84–1.40)	0.96 (0.76–1.20)	Reference	1.21 (0.95–1.56)	**1.39 (1.02–1.90)**	1.61 (0.83–3.09)	1.03 (1.00–1.06)	0.09	$P = 0.909$, 0	$P = 0.761$, 0
HR (model 1) excluding early cases[a]	0.83 (0.53–1.30)	1.00 (0.78–1.30)	0.90 (0.72–1.13)	Reference	**1.31 (1.03–1.67)**	**1.47 (1.08–1.98)**	1.65 (0.86–3.17)	**1.05 (1.02–1.08)**	0.001	$P = 0.706$, 0	$P = 0.785$, 0
HR (model 2) excluding early cases[b]	0.87 (0.55–1.36)	1.02 (0.78–1.32)	0.91 (0.73–1.15)	Reference	**1.30 (1.02–1.66)**	**1.45 (1.07–1.97)**	1.63 (0.85–3.13)	**1.05 (1.02–1.08)**	0.002	$P = 0.656$, 0	$P = 0.839$, 0
HR (model 3) excluding early cases[c]	0.84 (0.50–1.41)	1.08 (0.82–1.44)	0.92 (0.72–1.18)	Reference	1.23 (0.94–1.60)	**1.40 (1.01–1.95)**	1.68 (0.84–3.37)	**1.04 (1.01–1.07)**	0.02	$P = 0.695$, 0	$P = 0.621$, 0
Distal colon cancer[d]											
Number of cases (n =)	46	155	232	252	160	82	19				
CR (per 100 000)	50.58	54.1	49.9	54.31	62.16	63.03	66.15				
HR (model 1) overall[a]	0.91 (0.66–1.26)	0.97 (0.79–1.18)	0.88 (0.73–1.05)	Reference	1.18 (0.97–1.45)	1.27 (0.99–1.63)	**1.77 (1.10–2.87)**	1.00 (1.00–1.01)	0.776	**$P = 0.002$, 69.5**	$P = 0.262$, 22.8
HR (model 2) overall[b]	0.92 (0.66–1.28)	0.95 (0.77–1.16)	0.87 (0.73–1.04)	Reference	1.19 (0.97–1.45)	**1.28 (1.00–1.65)**	**1.80 (1.11–2.92)**	**1.05 (1.03–1.08)**	<0.001	**$P < 0.001$, 100**	$P = 0.293$, 18.6
HR (model 3) overall[c]	1.01 (0.70–1.46)	0.94 (0.76–1.18)	0.83 (0.68–1.01)	Reference	1.20 (0.97–1.48)	**1.33 (1.02–1.73)**	**1.77 (1.06–3.00)**	**1.05 (1.03–1.08)**	<0.001	$P = 0.627$, 0	$P = 0.126$, 47.5

Table 2. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	P, I^2 (%) For trend	For the highest category
HR (model 1) excluding early cases[a]	0.89 (0.62–1.29)	1.01 (0.81–1.26)	0.93 (0.77–1.14)	Reference	1.21 (0.97–1.51)	**1.37 (1.05–1.80)**	**2.20(1.35–3.66)**	**1.05 (1.03–1.08)**	<0.001	P = 0.584, 0	P = 0.443, 0
HR (model 2) excluding early cases[b]	0.90 (0.62–1.30)	0.99 (0.80–1.24)	0.92 (0.76–1.12)	Reference	1.21 (0.97–1.51)	**1.38 (1.05–1.82)**	**2.24 (1.35–3.69)**	**1.05 (1.03–1.08)**	<0.001	P = 0.598, 0	P = 0.445, 0
HR (model 3) excluding early cases[c]	1.00 (0.67–1.52)	1.00 (0.79–1.28)	0.87 (0.70–1.08)	Reference	1.22 (0.97–1.55)	**1.44 (1.08–1.91)**	**2.24 (1.31–3.82)**	**1.06 (1.03–1.08)**	<0.001	P = 0.728, 0	P = 0.174, 42.8
Rectal cancer											
Number of cases (n =)	59	179	325	284	158	80	26				
CR (per 100 000)	64.87	62.48	69.9	61.21	61.38	61.49	90.52				
HR (model 1) overall[a]	0.93 (0.70–1.24)	0.97 (0.80–1.17)	1.10 (0.94–1.29)	Reference	1.03 (0.85–1.25)	1.16 (0.89–1.49)	**1.79 (1.19–2.69)**	1.02 (1.00–1.04)	0.142	P = 0.979, 0	P = 0.467, 0
HR (model 2) overall[b]	0.92 (0.69–1.23)	0.95 (0.79–1.15)	1.09 (90.93–1.28)	Reference	1.04 (0.86–1.27)	1.17 (0.91–1.52)	**1.85 (1.23–2.78)**	1.02 (1.00–1.04)	0.102	P = 0.980, 0	P = 0.450, 0
HR (model 3) overall[c]	0.91 (0.65–1.27)	0.98 (0.80–1.21)	1.12 (0.94–1.33)	Reference	1.12 (0.91–1.37)	1.20 (0.91–1.58)	1.57 (0.97–2.53)	1.02 (0.99–1.04)	0.202	P = 0.924, 0	P = 0.256, 24.9
HR (model 1) excluding early cases[a]	0.96 (0.69–1.32)	0.88 (0.71–1.10)	1.03 (0.86–1.23)	Reference	1.05 (0.85–1.30)	1.19 (0.89–1.58)	**1.87 (1.21–2.88)**	**1.03 (1.00–1.05)**	0.035	P = 0.582, 0	P = 0.701, 0
HR (model 2) excluding early cases[b]	0.95 (0.69–1.31)	0.86 (0.70–1.07)	1.01 (0.85–1.21)	Reference	1.06 (0.86–1.32)	1.21 (0.90–1.61)	**1.92 (1.25–2.97)**	**1.03 (1.00–1.05)**	0.023	P = 0.517, 0	P = 0.688, 0
HR (model 3) excluding early cases[c]	0.97 (0.67–1.41)	0.89 (0.70–1.14)	1.03 (0.84–1.26)	Reference	1.13 (90.90–1.42)	1.20 (0.88–1.65)	1.52 (0.91–2.55)	**1.03 (1.00–1.05)**	0.069	P = 0.504, 0	P = 0.721, 0

[a]Adjusted for age and area.

[b]Adjusted for age, area, smoking (never, former, current <20 pieces/day, current ≥20 pieces/day or unknown) and drinking (never, <1 week/day, current <23 g/day, 23 to <46 g/day, 46 to <69, 69 to <92 and ≥92 g/day).

[c]Adjusted for age, area, smoking (never, former, current <20 pieces/day, current ≥20 pieces/day or unknown), drinking (never, <1 week/day, current <23 g/day, 23 to <46 g/day, 46 to <69, 69 to <92 and ≥92 g/day) and total energy, red meat in quartile, dietary fiber in quartile, calcium intake in quartile, folate intake in quartile and recreational physical exercise. This model is only for JPHC1, JPHC2, JACC, MIYAGI1, OHSAKI and Takayama based on availability of adjusting factors.

[d]Those whose ICD-O-3 topology code was C18.8 were excluded from analysis.

BMI, body mass index; 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; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; CR, crude risk.

HRs values in bold show statistical significance.

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Table 3. Pooled analysis for BMI and colorectal cancer risk according to subsite[d] (female)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
Number of subjects (*n* =)	14 467	32 423	48 060	42 249	25 623	15 830	4805				
Person-years (*n* =)	146 751.95	353 214.1	537 047.03	478 890.4	291 734.7	180 691.72	54 564.75				
Colorectal cancer											
Number of cases (*n* =)	130	314	480	438	301	192	69				
CR (per 100 000)	88.58	88.9	89.38	91.46	103.18	106.26	126.46				
HR1 overall[a]	0.93 (0.76–1.14)	1.00 (0.86–1.16)	1.00 (0.88–1.14)	Reference	1.08 (0.93–1.25)	1.10 (0.93–1.31)	**1.31 (1.01–1.69)**	**1.02 (1.01–1.04)**	0.002	*P* = 0.387, 5.7	*P* = 0.894, 0
HR2 overall[b]	0.93 (0.76–1.13)	1.00 (0.86–1.16)	1.00 (0.88–1.14)	Reference	1.06 (0.92–1.23)	1.10 (0.93–1.31)	**1.30 (1.00–1.68)**	**1.02 (1.00–1.03)**	0.032	*P* = 0.505, 0	*P* = 0.870, 0
HR3 overall[c]	0.91 (0.73–1.15)	0.95 (0.80–1.13)	1.01 (0.88–1.17)	Reference	1.07 (0.91–1.25)	1.06 (0.88–1.28)	1.17 (0.87–1.57)	**1.07 (1.05–1.08)**	<0.001	***P* < 0.001, 97.9**	*P* = 0.854, 0
HR1 excluding early cases[a]	0.94 (0.74–1.18)	1.04 (0.88–1.22)	1.01 (0.87–1.17)	Reference	**1.19 (1.01–1.40)**	**1.22 (1.01–1.47)**	1.23 (0.91–1.66)	**1.02 (1.01–1.04)**	0.007	*P* = 0.909, 0	*P* = 0.941, 0
HR2 excluding early cases[b]	0.93 (0.74–1.18)	1.03 (0.87–1.21)	1.01 (0.87–1.17)	Reference	**1.18 (1.00–1.38)**	**1.21 (1.00–1.47)**	1.21 (0.90–1.64)	**1.02 (1.00–1.04)**	0.015	*P* = 0.749, 0	*P* = 0.935, 0
HR3 excluding early cases[c]	0.98 (0.75–1.27)	0.97 (0.81–1.18)	1.00 (0.85–1.17)	Reference	1.17 (0.98–1.40)	1.16 (0.94–1.42)	1.12 (0.81–1.57)	**1.02 (1.00–1.03)**	0.101	*P* = 0.786, 0	*P* = 0.874, 0
Colon cancer											
Number of cases (*n* =)	76	215	330	512	217	136	48				
CR (per 100 000)	51.79	60.87	61.45	106.91	74.38	75.27	87.97				
HR1 overall[a]	0.80 (0.62–1.04)	1.00 (0.83–1.20)	1.03 (0.88–1.21)	Reference	**1.19 (1.00–1.43)**	1.22 (0.99–1.50)	**1.40 (1.03–1.91)**	**1.04 (1.02–1.06)**	<0.001	***P* = 0.018, 58.6**	*P* = 0.902, 0
HR2 overall[b]	0.80 (0.61–1.04)	1.00 (0.83–1.20)	1.03 (0.88–1.21)	Reference	1.18 (0.99–1.41)	1.22 (0.99–1.51)	**1.39 (1.02–1.90)**	**1.04 (1.03–1.06)**	<0.001	***P* = 0.002, 69.4**	*P* = 0.862, 0
HR3 overall[c]	0.71 (0.52–0.97)	0.87 (0.71–1.07)	1.00 (0.84–1.19)	Reference	**1.21 (1.02–1.44)**	1.11 (0.88–1.39)	1.18 (0.83–1.68)	**1.03 (1.01–1.05)**	0.003	*P* = 0.833, 0	*P* = 0.984, 0
HR1 excluding early cases[a]	0.83 (0.62–1.12)	1.00 (0.80–1.22)	1.03 (0.86–1.23)	Reference	**1.27 (1.04–1.54)**	**1.29 (1.03–1.61)**	**1.47 (1.05–2.06)**	**1.04 (1.02–1.06)**	<0.001	*P* = 0.753, 0	*P* = 0.933, 0

Table 3. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m²	19 to <21 kg/m²	<23 kg/m²	23 to <25 kg/m²	25 to <27 kg/m²	27 to <30 kg/m²	30 kg/m²	Trend (per 1 kg/m²)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR2 excluding early cases[b]	0.83 (0.62–1.12)	0.99 (0.80–1.21)	1.02 (0.86–1.22)	Reference	**1.25 (1.03–1.52)**	**1.29 (1.03–1.61)**	**1.46 (1.04–2.04)**	**1.04 (1.02–1.06)**	<0.001	*P* = 0.757, 0	*P* = 0.907, 0
HR3 excluding early cases[c]	0.83 (0.59–1.16)	0.86 (0.68–1.09)	0.98 (0.80–1.19)	Reference	**1.24 (1.00–1.53)**	1.19 (0.93–1.53)	1.31 (0.89–1.91)	**1.04 (1.02–1.06)**	0.001	*P* = 0.687, 0	*P* = 0.858, 0
Proximal colon cancer											
Number of cases (*n* =)	33	103	176	182	107	84	25				
CR (per 100 000)	22.49	29.16	32.77	38	36.68	46.49	45.82				
HR1 overall[a]	0.76 (0.51–1.13)	0.98 (0.76–1.27)	1.07 (0.86–1.33)	Reference	1.09 (0.84–1.40)	**1.34 (1.02–1.77)**	1.40 (0.92–2.15)	**1.04 (1.01–1.06)**	0.002	*P* = 0.788, 0	*P* = 0.596, 0
HR2 overall[b]	0.77 (0.52–1.14)	0.99 (0.76–1.28)	1.07 (0.86–1.33)	Reference	1.06 (0.82–1.38)	**1.35 (1.02–1.77)**	1.38 (0.89–2.13)	**1.04 (1.01–1.06)**	0.002	*P* = 0.771, 0	*P* = 0.548, 0
HR3 overall[c]	0.67 (0.43–1.05)	0.85 (0.64–1.13)	1.04 (0.83–1.31)	Reference	1.01 (0.77–1.32)	1.20 (0.90–1.61)	1.26 (0.79–1.99)	**1.03 (1.01–1.06)**	0.009	*P* = 0.757, 0	*P* = 0.633, 0
HR1 excluding early cases[a]	0.81 (0.53–1.25)	0.95 (0.71–1.26)	0.99 (0.78–1.26)	Reference	1.13 (0.87–1.48)	**1.36 (1.02–1.83)**	1.56 (0.99–2.43)	**1.05 (1.02–1.07)**	<0.001	*P* = 0.641, 0	*P* = 0.460, 0
HR2 excluding early cases[b]	0.82 (0.53–1.26)	0.95 (0.71–1.26)	0.99 (0.78–1.26)	Reference	1.11 (0.85–1.46)	**1.36 (1.02–1.83)**	1.52 (0.96–2.40)	**1.05 (1.02–1.07)**	<0.001	*P* = 0.629, 0	*P* = 0.406, 3.1
HR3 excluding early cases[c]	0.79 (0.50–1.27)	0.82 (0.60–1.11)	0.95 (0.74–1.23)	Reference	1.06 (0.80–1.42)	1.25 (0.92–1.72)	1.38 (0.85–2.26)	**1.04 (1.02–1.07)**	0.002	*P* = 0.636, 0	*P* = 0.394, 3.5
Distal colon cancer											
Number of cases (*n* =)	23	84	115	252	76	40	19				
CR (per 100 000)	15.67	23.78	21.41	52.62	26.05	22.14	34.82				
HR1 overall[a]	0.73 (0.46–1.17)	1.09 (0.80–1.47)	1.01 (0.77–1.33)	Reference	1.24 (0.91–1.69)	1.08 (0.74–1.58)	1.76 (1.06–2.92)	1.03 (1.00–1.06)	0.071	*P* = 0.643, 0	*P* = 0.847, 0
HR2 overall[b]	0.72 (0.45–1.15)	1.08 (0.80–1.46)	1.00 (0.76–1.31)	Reference	1.24 (0.91–1.69)	1.07 (0.74–1.56)	1.76 (1.06–2.91)	1.03 (1.00–1.06)	0.063	*P* = 0.659, 0	*P* = 0.853, 0
HR3 overall[c]	0.78 (0.46–1.31)	1.03 (0.73–1.44)	0.98 (0.72–1.32)	Reference	1.31 (0.93–1.84)	1.08 (0.71–1.65)	1.42 (0.76–2.66)	1.02 (0.99–1.05)	0.258	*P* = 0.630, 0	*P* = 0.745, 0

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Table 3. (*Continued*)

	BMI, HR (95% CI)									Heterogeneity	
	<19 kg/m^2	19 to <21 kg/m^2	<23 kg/m^2	23 to <25 kg/m^2	25 to <27 kg/m^2	27 to <30 kg/m^2	30 kg/m^2	Trend (per 1 kg/m^2)	Trend *P*	*P*, I^2 (%) For trend	For the highest category
HR1 excluding early cases[a]	0.94 (0.56–1.59)	1.11 (0.78–1.58)	1.07 (0.79–1.46)	Reference	**1.47 (1.05–2.07)**	1.28 (0.85–1.92)	**1.84 (1.03–3.27)**	1.03 (1.00–1.06)	0.062	*P* = 0.337, 11.9	*P* = 0.718, 0
HR2 excluding early cases[b]	0.93 (0.55–1.57)	1.10 (0.77–1.57)	1.06 (0.78–1.44)	Reference	**1.47 (1.05–2.06)**	1.28 (0.85–1.92)	**1.85 (1.04–3.28)**	1.03 (1.00–1.07)	0.053	*P* = 0.360, 9.1	*P* = 0.760, 0
HR3 excluding early cases[c]	1.05 (0.58–1.91)	1.04 (0.69–1.56)	1.03 (0.73–1.46)	Reference	**1.62 (1.12–2.35)**	1.28 (0.80–2.06)	1.85 (0.91–3.78)	**1.04 (1.01–1.08)**	0.011	*P* = 0.112, 44.0	*P* = 0.472, 0
Rectal cancer											
Number of cases (*n* =)	53	97	147	284	80	54	20				
CR (per 100 000)	36.12	27.46	27.37	59.3	27.42	29.89	36.65				
HR1 overall[a]	1.31 (0.95–1.80)	0.99 (0.76–1.29)	0.94 (0.75–1.18)	Reference	0.89 (0.67–1.18)	0.93 (0.68–1.28)	1.35 (0.83–2.18)	1.00 (0.98–1.03)	0.946	*P* = 0.677, 0	*P* = 0.472, 0
HR2 overall[b]	1.31 (0.95–1.81)	0.98 (0.76–1.27)	0.94 (0.74–1.18)	Reference	0.88 (0.66–1.17)	0.92 (0.67–1.27)	1.33 (0.82–2.15)	1.00 (0.99–1.00)	0.158	*P* = 0.894, 0	*P* = 0.478, 0
HR3 overall[c]	1.44 (0.99–2.08)	1.12 (0.84–1.50)	1.05 (0.81–1.35)	Reference	0.88 (0.64–1.20)	0.99 (0.70–1.39)	1.39 (0.81–2.39)	1.00 (0.97–1.03)	0.785	*P* = 0.293, 18.5	*P* = 0.397, 0
HR1 excluding early cases[a]	1.35 (0.93–1.96)	1.07 (0.80–1.42)	0.94 (0.72–1.22)	Reference	1.04 (0.76–1.42)	1.05 (0.74–1.49)	1.13 (0.62–2.04)	0.98 (0.95–1.01)	0.23	*P* = 0.882, 0	*P* = 0.625, 0
HR2 excluding early cases[b]	1.35 (0.93–1.97)	1.06 (0.80–1.42)	0.94 (0.72–1.22)	Reference	1.03 (0.75–1.40)	1.04 (0.73–1.48)	1.11 (0.61–2.01)	0.98 (0.95–1.01)	0.203	*P* = 0.876, 0	*P* = 0.623, 0
HR3 excluding early cases[c]	1.52 (0.99–2.34)	1.23 (0.89–1.70)	1.05 (0.78–1.40)	Reference	1.00 (0.71–1.41)	1.13 (0.77–1.67)	1.02 (0.50–2.06)	**0.97 (0.94–1.00)**	0.048	*P* = 0.984, 0	*P* = 0.562, 0

[a]Adjusted for age and area.

[b]Adjusted for age, area, smoking (never, former, current or unknown) and drinking (never, <1 week/day, current <23 g/day, ≥23 g/day).

[c]Adjusted for age, area, smoking (never, former, current or unknown), drinking (never, <1 week/day, current <23 g/day, ≥23 g/day) and total energy, red meat in quartile, dietary fiber in quartile, calcium intake in quartile, folate intake in quartile and recreational physical exercise. This model is only for JPHC1, JPHC2, JACC, MIYAGI1, OHSAKI and Takayama based on availability of adjusting factors.

[d]Those whose ICD-O-3 topology code was C18.8 were excluded from analysis.

BMI, body mass index; 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; AICHI, Aichi Cohort Study; OHSAKI, Ohsaki Cohort Study; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; CR, crude risk.

>300 000 Japanese, we have demonstrated that higher BMI increases the risk of colorectal cancer in Japan. The association was stronger in males than in females and the pattern of association between BMI and risk were stronger in colon than in rectum. Our finding is consistent with the former meta-analysis using studies mainly from Western countries [12–14]. A recent meta-analysis of 58 studies showed that HRs for colorectal cancer by 5 kg/m^2 BMI increase in Western populations (1.23 for North American population and 1.13 in European population) [14]. This is almost comparable with our finding in this pooled analysis (1.16 for 5 kg/m^2 increase). In terms of sex difference, the study showed HRs for BMI ≥30 kg/m^2 as 1.53 for men and 1.26 for females [14] and these were similar in our analysis (Tables 1 and 2). Similarly, a heterogeneity by subsite is comparable between ours and the published meta-analyses.

To date, only a limited numbers of prospective studies in Japan have been conducted to evaluate association between colorectal cancer and BMI [8, 20, 22, 23]. One reported significant positive association only in colon cancer in women [22], another reported significant association with colorectal cancer in women [23], while the rest reported positive association in colorectal and colon cancer in men [8, 20]. The reason for this heterogeneity might partly be due to limited statistical power to detect the association in each study. In this sense, an approach of this study might resolve statistical limitations in each of individual study result of this study is very important in terms of having stable estimation in this topic. Moreover, very limited evidence in Asian population warrants an importance of findings in this study in planning of cancer prevention.

In last several decades, average BMI in Japanese population increased constantly [2, 3], although proportion of obesity has been low compared with Western populations. Taken concrete association between colorectal cancer risk and BMI in this study, constant BMI increase in Japanese population over decades is one of the unequivocal reasons for rapid increase on colorectal cancer incidence in Japan observed until early 1990s [30]. In other words, reducing burden of excess BMI in Japanese population can prevent substantial proportion of colorectal cancer.

PAF is one of the indicators for proportion of preventable fraction in certain population. In this study, PAFs by BMI ≥25 kg/m^2 were revealed to be 3.6% for males and 2.6% for females, indicating that potential quantitative impacts of reducing BMI <25 on colorectal cancer in Japanese population. This is smaller than those estimated in Western population [31]. Renehan et al. recently estimated PAF of BMI ≥25 kg/m^2 on colon (10.92% for males and 2.57% for females) and rectal cancer (5.05 for males) by using data of 30 countries in Europe. This difference might be reasonable because there is large difference in prevalence of obesity or overweight between Japanese and Western population [1–3] because HRs for 5 kg/m^2 BMI increase in Western populations (1.23 for North American population and 1.13 in European population) [14] are almost comparable with our finding in this pooled analysis (1.16 for 5 kg/m^2 increase). Considering a rapid increase in the proportion of overweight and obesity in Asian population [1], we may imagine the increase of colorectal cancer burden in Asia in near future. That is to say expected increase of colorectal cancer will be prevented if the appropriate program for obesity will be applied.

The present study has several strengths. It included most of the ongoing, large-scale prospective cohorts in Japan. Total numbers of subjects in this analysis is very large warranting statistical power to detect association between BMI and colorectal cancer risk. In addition, the birth generation of the study subjects in the cohorts overlapped. Therefore, pooling of these cohorts allows for stable summary quantitative estimates of the effect of BMI on premature death in middle-aged and elderly Japanese adults. The use of incidence rather than mortality as an end point is advantageous enabling directly referring risk contribution by BMI. At the same time, because this study was not based on a meta-analysis of published studies, the possibility of publication bias is small. In the studies included in this pooled analysis, BMI was measured before colorectal cancer incidence, which precludes the possibility of selection and recall bias. Most of the studies used validated questionnaires or equivalent ones for BMI measurement; therefore, impact of error in the analysis can be limited if it exists. In addition, the categories for BMI and the covariates used were identical across study, which removes a potential source of heterogeneity that can occur when conducting a meta-analysis of published studies.

However, there are several limitations that warrant consideration. We observed significant heterogeneity of association in colorectal cancer in men. Although we applied random effects model, an effect of this on summary estimates can be undeniable. As our analyses were conducted using only a baseline questionnaire, we were unable to consider changes over time in BMI. Similar is true to change of potential confounders in the analysis. Although we considered potential confounders in the analysis, potential residual confounding cannot be completely ruled out. Lastly, we estimated PAFs based upon distribution of BMI within cohorts in this analysis. Assuming potential selection bias of subjects in the studies pooled, our PAFs estimated in this analysis could be under/overestimated ones. Therefore, PAFs should be carefully interpreted.

In conclusion, we found a positive and a significant association between BMI and colorectal cancer risk by pooling of data from cohort studies with considerable number of subjects among Japanese population. This association was stronger in colon, especially in proximal colon, relative to rectum. Males showed stronger association than females. This information is important in cancer control planning by prevention of obesity especially in Asian population.

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disclosure

The authors have declared no conflicts of interest.

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

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Although alcohol drinking 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 alcohol drinking and esophageal cancer among the Japanese population. Original data were obtained from MEDLINE, searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient') and the magnitude of association ('strong', 'moderate', 'weak' or 'no association'), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer. We identified four cohort studies and nine case–control studies. All cohort studies and case–control studies showed strong positive associations between esophageal cancer and alcohol drinking. All cohort studies and six case–control studies showed that alcohol drinking had the dose- or frequency-response relationships with esophageal cancer. In addition, four case–control studies showed that acetaldehyde dehydrogenase Glu504Lys polymorphism had strong effect modification with alcohol drinking. We conclude that there is convincing evidence that alcohol drinking increases the risk of esophageal cancer in the Japanese population.

Key words: systematic review – epidemiology – alcohol drinking – esophageal cancer – Japanese

INTRODUCTION

The association between alcohol drinking and the risk of esophageal cancer has been consistently reported from all over the world. In the most recent evaluation by the International Agency for Research on Cancer (IARC), ethanol in alcoholic beverages are evaluated as Group 1: carcinogenic to humans (1,2). In the second report published by the World Cancer Research Fund and the American Institute for Cancer Research, the panel judged that alcoholic drinks are convincing cause of esophageal cancer (3). Thus, alcohol drinking was a well-established risk factor for esophageal cancer. IARC referred to acetaldehyde, an oxidative

metabolite of ethanol, as a potential causative agent behind alcohol-induced carcinogenesis based on evidence about interaction between alcohol consumption and acetaldehyde dehydrogenase (ALDH2) enzyme gene polymorphisms for the risk (2,4).

On the other hand, the risk of esophageal cancer might be varied among geographic areas and clustered in specific areas such as 'Esophageal cancer belt' (5). The types of beverages commonly consumed among Japanese differ from those among other populations. Other difference is histology of esophageal cancer. Most of the esophageal cancer cases are squamous cell carcinoma among the Japanese in contrast to adenocarcinoma among Western population (6–9). In addition, ethnicity is another cause of difference. The sensitivity to alcohol might differ between each ethnicity because the distribution of genetic polymorphisms was different. For example, *ALDH2* Glu504Lys polymorphism affects the metabolism of acetaldehyde. Those with *ALDH2* Lys allele show a high concentration of blood acetaldehyde after alcohol drinking due to the low catalytic activity of ALDH2 enzyme. Therefore, the magnitude of the association between alcohol drinking and esophageal cancer among the Japanese population might differ from the other regions.

We review epidemiological studies on alcohol drinking and esophageal cancer risk among the Japanese. This report is one of a series of articles by our research group (10–23), which is investigating the association between lifestyle and the major types of cancer in Japan.

PATIENTS AND METHODS

The details of the evaluation method have been described elsewhere (10). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi* (*Japana Centra Revuo Medicina*) databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between alcohol drinking and esophageal cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichusi* database) to January 2010, including papers in press if available, were identified using the following as keywords: alcohol, 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, and incidence was also given priority in a single publication describing both incidence and mortality.

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 (24), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (10): 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). The final judgment is made based on the consensus of research group members.

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, meta-analysis was conducted to obtain summary estimates of the association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever drinkers with never or non-drinkers were included in the

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

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

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

meta-analysis. In case the subject study reported RRs separately according to multiple drinking status or levels, we estimated summary RR for ever drinkers relative to never drinkers 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 (25), with the model used to determine summary RR and its 95% CI, namely a random or fixed effect model, selected according to the SS in the Q statistic. Publication bias was assessed by using funnel plot and Egger's test (26). 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 one cohort study (27) and one case–control study (28) due to the analysis of the overlapping data sets, we identified four cohort studies (29–32) (Table 2) and nine case–control studies (4,33–40) (Table 3). Of those cohort studies, one (29) presented the results by sex and three (30–32) presented the results for men only. Among case–control studies, one (33) presented the results by sex, three (4,38,40) for men and women combined, three (34–36) for men only and two (37,39) for women only.

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 4 and 5, respectively. All studies showed a strong association between alcohol drinking and esophageal cancer. Moreover, the dose- or frequency-response relationships between alcohol drinking and esophageal cancer risk were shown in all cohort studies (29–32) and six case–control studies (4,34–37,40).

Additionally, two cohort studies (29,30) and one case–control study (34) investigated the type of alcoholic beverages and calculated the odds ratio (OR) for esophageal cancer by each beverage. However, the differences between the types of alcoholic beverages were not obvious. Four case–control studies (4,36,37,40) evaluated the OR for esophageal cancer by *ALDH2* Glu504Lys genotype. Subjects with *ALDH2* Glu/Lys genotype showed significantly higher ORs than those with *ALDH2* Glu/Glu genotype in these case–control studies. Facial flushing after alcohol consumption has been hypothesized for potential risk factor for esophageal cancer, because facial flushing has been considered as surrogate for *ALDH2* Glu504Lys polymorphisms (37,41–43). However, recent prospective study and large scale case–control study showed its limitation for the purpose (32,40).

Lastly, we conducted a meta-analysis to clarify the magnitude of alcohol drinking among Japanese (Fig. 1). One study was excluded because of the different reference category (4). Random effect model was selected for the meta-analysis because heterogeneity tested for Q statistics was significant ($Q = 53.90$, $P < 0.001$). Egger's test to evaluate publication bias was not significant ($P = 0.713$). Ever drinkers had significantly higher summary RR than never drinkers (RR 3.30, 95% CI 2.30–4.74). Although smoking often confounds with alcohol drinking, smoking was not adjusted in several studies. We conducted the meta-analysis only among the studies adjusted for smoking by using random effect model (32,33,39,40). After excluding eight studies without adjustment for smoking, summary RR was 3.36 (95% CI, 1.66–6.78) and heterogeneity was significant ($Q = 17.36$, $P = 0.001$).

There were several potential limitations in the Japanese studies reviewed here. One methodological issue was assessment of drinking status. Information on alcohol consumption was investigated by questionnaire in all cohort and case–control studies. However, the definition and categorization of drinking dose and frequency were different between studies. In addition, it is necessary to consider the misclassification. These might attenuate the association between alcohol drinking and esophageal cancer risk. In contrast, recall bias might intensify the association. In spite of the methodological issues, we observed strong association and clear dose- or frequency-response relationship between alcohol drinking and esophageal cancer risk.

Another methodological issue was *ALDH2* Glu504Lys polymorphism. *ALDH2* Lys allele is prevalent in Japanese, while the frequency is very rare in Caucasians. This polymorphism would cause large individual difference for esophageal cancer risk by modification of acetaldehyde metabolism as well as drinking behavior (44,45). Although *ALDH2* Glu504Lys polymorphism was investigated in some case–control studies, no cohort study has examined the polymorphism. Therefore, *ALDH2* Glu504Lys polymorphism should be considered on the esophageal cancer studies hereafter.

Lastly, the meta-analysis showed that ever drinkers had a significantly higher risk for esophageal cancer than never drinkers. Because of the different alcohol consumption categories, we could not see the dose- or frequency-response relationships. The heterogeneity across studies is likely to be due to the different alcohol exposure levels by characteristics of subjects in each study, such as birth cohort, age, sex and base-population. Therefore, a pooled analysis using common alcohol consumption categories is warranted.

EVALUATION OF EVIDENCE ON ALCOHOL DRINKING 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 alcohol drinking increases the risk of esophageal cancer in Japanese population.

Table 2. Alcohol drinking and esophageal cancer risk, cohort studies among Japanese population

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
Hirayama (29)	1965–1981 (17 years)	122 261 men, 142 857 women ≥40 years old	Population-based Kagoshima Okayama Hyogo Osaka Aichi Miyagi	Death	438 men	Alcohol drinking[a]			Not described	Age	Follow-up by death certificates and residential registry CIs were 90%
						Non-drinker	NA	1.0			
						Rare	NA	0.85 (0.61–1.19)			
						Occasional	NA	1.12 (0.87–1.46)			
						Daily	NA	2.30 (1.84–2.87)			
						Type of alcoholic beverage					
						Non-drinker	NA	1.0			
						Sake	NA	2.32 (1.81–2.97)			
						Shochu	NA	3.11 (2.38–4.08)			
						Beer	NA	2.31 (1.53–3.48)			
						Whisky	NA	4.10 (2.28–7.37)			
						Other	NA	2.00 (0.54–7.37)			
					147 women	Alcohol drinking[a]			Not described		
						Non-drinker	NA	1.0			
						Rare	NA	0.82 (0.50–1.35)			
						Occasional	NA	1.04 (0.58–1.89)			
						Daily	NA	2.41 (1.04–5.57)			
						Type of alcoholic beverage					
						Non-drinker	NA	1.0			
						Sake	NA	2.84 (0.98–8.23)			
						Shochu	NA	4.23 (1.13–15.8)			
						Beer	NA	9.29 (3.14–27.45)			
						Whisky	NA	NA			

						Other	NA	NA			
Sakata et al. (30)	1988–1999 (12 years)	46 465 men 40–79 years	Population-based 45 areas in Japan JACC study	Death	100 men	Alcohol intake status			Not described	Age and centers	One unit contains about 22 g of alcohol
						Non-drinker	9	1.0			
						Ex-drinker	8	2.43 (0.91–6.47)			
						Drinker	83	2.40 (1.20–4.80)			
						Alcohol units consumed per day[a]			$P = 0.028$		
						Non-drinker	9	1.0			
						<1.0 units/day	2	1.47 (0.28–7.68)			
						1.0–1.9	16	1.58 (0.65–3.86)			
						2.0–2.9	31	3.74 (1.62–8.66)			
						≥3.0	18	6.39 (2.54–16.12)			
						Years of alcohol drinking			$P = 0.100$		
						Non-drinker	9	1.0			
						≤25.0 years	14	1.71 (0.64–4.60)			
						25.1–35.0 years	19	3.23 (1.32–7.92)			
						35.1–45.0 years	18	3.23 (1.33–7.81)			
						≥45.1	7	2.77 (0.85–9.03)			
						Cumulative amount of alcohol intake			$P = 0.089$		
						Non-drinker	9	1.0			
						1–29.9 unit-year	4	0.68 (0.19–2.42)			
						30–39.9 unit-year	6	2.31 (0.75–7.06)			
						≥40.0 unit-year	46	3.80 (1.70–8.46)			
						Type of alcohol			Not described		
						Non-drinker	9	1.0			
						Sake	48	2.72 (1.22–6.08)			
						Shochu	15	3.40 (1.33–8.68)			
						Beer	17	1.42 (0.58–3.52)			
						Whisky	9	2.60 (0.91–7.41)			
						Wine	6	6.24 (1.53–25.37)			
Ishikawa et al. (31)	Cohort 1 1984–1992	Cohort 1: 9008 men 40 years or older	Population-based Miyagi Pref.	Incidence	Cohort 1: 38 cases	Cohort 1					

Continued

Table 2. *Continued*

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
						Never	2	1.0	$P = 0.017$	Adjusted for age, alcohol drinking, green tea, coffee and black tea	
						Former	6	2.31 (0.68–7.83)			
	Cohort 2 1990–1997	Cohort 2: 17 715 men 40–64 years				Daily	11	2.70 (1.20–6.06)			
					Cohort 2	Cohort 2					
					40 cases	Never	2	1.0	$P = 0.007$		
						Former	6	0.54 (0.06–4.04)			
						Daily	11	2.77 (1.26–6.09)			
						Pooled 1 and 2[a]					
						Never	2	1.0	$P = 0.0002$		
						Former	6	1.55 (0.58–4.14)			
						Daily	11	2.73 (1.55–4.81)			
Ishiguro et al. (32)	Cohort 1 1990–2004	Cohort 1 + 2, 60 876 men	Population-based JPHC study	Incidence	Cohort 1 + 2 215 cases	Alcohol consumption[a]					
						Non-drinker	24	1.0	$P = 0.001$ among drinkers	Adjusted for age at baseline, area, BMI, hot foods/ drink preference, smoking status and flushing	
	Cohort 2 1993–2004	40 years or older				Occasional	5	0.60 (0.21–1.75)			
						<149 g ethanol/w	41	1.64 (0.96–2.78)			
						150–299	55	2.59 (1.57–4.29)			
						300+	90	4.64 (2.88–7.48)			

NA, not available, CI, confidence interval; BMI, body mass index.
[a]Categories from which the magnitude of association was judged.

Table 3. Alcohol drinking and esophageal cancer risk, case–control studies among Japanese population

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Sasaki et al. (33)	1974–1979	Hospital-based (three major hospitals in Nagoya and two in Wakayama)	Case: those admitted in subject hospitals	201 (Nagoya: male 91, female 28, Wakayama: male 54, female 28) (age not described)	403 (Nagoya: male 170, female 57, Wakayama: male 115, female 61) (age not described)	Sake drinking in evenings[a]		Not described	Matched for age, sex, hospital and time of admission. Adjusted for smoking	
			Controls: non-digestive tract cancer patients in the same hospitals			Nagoya (male)				
						No	1.0			
						Yes	2.1 (1.2–3.6)			
						Nagoya (female)				
						No	1.0			
						Yes	NA			
						Wakayama (male)				
						No	1.0			
						Yes	3.1 (1.4–6.6)			
						Wakayama (female)				
						No	1.0			
						Yes	NA			
Hanaoka et al. (34)	1989–1991	Hospital-based (seven hospitals Keio Univ., Iwate Medical College, Chiba Univ., Natl Shikoku Cancer Ctr, Aichi Cancer Ctr, Tokyo Women's Medical College)	Cases: males admitted to hospitals as histologically confirmed primary esophageal cancer age under 85	141 (age not described) (hospital not described) (male only)	141 (age not described) (hospital not described) (90 with malignant neoplasms, 51 with benign diseases) (male only)	Freq. of alcohol drinking[a]		$P = 0.0001$	Matched for age, sex and prefecture of residence	

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
			Controls: males admitted to same hospitals with diseases other than lung cancer, laryngeal cancer, hepatocellular carcinoma, pulmonary emphysema, chronic pancreatitis			Non-drinker	1.0			
						≤2 g/week	1.15 (0.34–3.83)		Conditional logistic model was used	
						3–4 g/week	3.10 (1.02–9.43)			
						Everyday	6.59 (2.51–17.35)			
						Alcohol consumption		$P = 0.0001$		
						≤53 g/week	1.0		Conditional logistic model was used	
						>53 g/week	2.19 (0.92–5.18)			
						>242 g/week	5.17 (2.13–12.55)			
						> 414 g/week	5.86 (2.42–14.17)			
						Type of alcoholic beverage (drinker only)				
						Beer	1.0	Not described		

						Whiskey	1.08 (0.38–3.12)		Adjusted for	
						Sake	1.17 (0.46–2.96)		freq. of drinking	
						Shochu	3.02 (0.99–9.19)			
Takezaki et al. (35)	1988–1997	Hospital-based (Aichi Cancer Center Hospital)	Cases: males visited to the hospital as having esophageal cancer	346 (age 40–79) (male only)	11 936 (age 40–79) (male only)	Drinking status		Not described	Not matched	
			Controls: visited to the hospital but not having any cancer			Almost never	1.0		Adjusted for age, season of visit, drinking and raw vegetable consumption	
						Former	4.4 (2.5–7.9)			
						Current	4.4 (2.9–6.7)			One drink equates to 180 ml Japanese sake equivalent
						Dose of alcohol consumption[a] (current drinkers)				
						almost never	1.0			
						<1.5 drinks/day	1.8 (1.1–2.9)			
						≥1.5 drinks/day	8.5 (5.6–13.1)			
						(former drinkers)				
						almost never	1.0			
						<1.5 drinks/day	3.0 (1.3–7.0)			
						≥1.5 drinks/day	6.9 (3.4–14.0)			
						Years after quitting				
						almost never	1.0			
						1–9 years	5.1 (2.6–10.0)			
						≥10 years	3.5 (1.4–9.1)			
Matsuo et al. (44)	1999–2000	Hospital-based (Aichi Cancer Center Hospital)	Cases: mixture of prevalent cases and incident cases of histologically confirmed esophageal cancer	102 (age 40–76) (male 86, female 16)	241 (age 39–69) (male 118, female 123)	Drinking status[a]			Not matched	Heavy drinking: more than two drinks + ≥5 times/group/week

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
			Controls: non-cancer subjects who visited gastroenterology clinics for gastroscopy			Non-heavy	1.0	Not described	Adjusted for age, sex and smoking	
						Heavy	13.5 (6.94–26.5)			
Yokoyama et al. (36)	2000–2001	Hospital-based (National Cancer Ctr, National Cancer Ctr East, Kawasaki Municipal hospital, National Osaka Hospital	Cases: hisotologically confirmed esophageal cancer cases within 3 years from registration (male)	234 (age 40–79) (all male)	634 (age 40–79) (all male)	Alcohol drinking[a]		Not described	Not matched	ORs for drinking not described
			Controls: cancer free males visited two Tokyo clinics for annual health check-up			Never/rare	1.0		Not adjusted	ORs were calculated from table in the original article
						Light	3.90 (1.41–13.3)			
						Moderate	17.1 (6.76–55.1)			Never/rare: <1 unit/week, light:1–8.9 units/week, moderate:9–17.9 units/week, heavy: ≥18 units/week, 1 unit: 22 g ethanol
						Heavy	39.0 (15.2–126.0)			
						Ex-drinker	10.2 (3.64–28.2)			

Takagi et al. (39)	1990–1999	Hospital-based (Hospitalized at Osaka Med. Ctr. for Cancer and Cardiovascular Disease)	Case: hospitalized and self-administered questionnaire limited to female Control: those selected from list of hospitalized patients who did not have cancer, benign tumor, cardiovascular disease and alcoholic liver diseases	34 female (age mean: 63.4)	178 female (age mean:53.1)	Drinking status[a]		Not described	Adjusted for smoking, hot food preference and frequency of tooth brushing	
						Never	1.0			
						Ever	3.0 (1.2–7.5)			
Yokoyama et al. (37)	2000–2004	Hospital-based (National Cancer Ctr, National Cancer Ctr East, Kawasaki Municipal hospital, National Osaka Hospital	Cases: hisotologically confirmed esophageal squamous cell carcinoma within 3 years from registration (female)	52 (age 40–79) (all female)	412 (age 40–79) (all female)	Alcohol drinking[a]		Not described	Not matched	Never/rare: <1 unit/week, light 1–8.9 units/week, moderate:9–17.9 units/week, heavy: ≥18 units/week, 1 unit 22 g ethanol
			Controls: cancer free males visited two Tokyo clinics for annual health check-up			Never/rare	1.0		Adjusted for age	
						Light	1.81 (0.81–4.05)			
						Moderate	3.97 (1.40–11.26)			
						Heavy	15.35 (4.85–48.62)			
						Ex-drinker	4.58 (1.25–16.79)			
						Strong alcohol beverage		$P = 0.012$		

Continued